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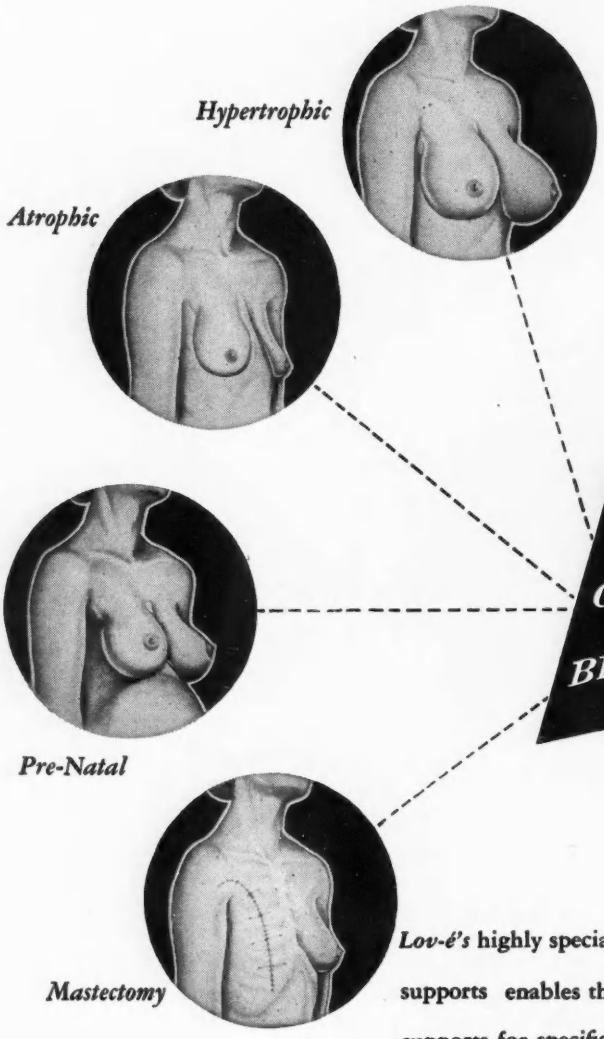

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California MEDICINE

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What's New in Communicable Diseases

EDWARD B. SHAW, M.D., *San Francisco*

THE essential concept of the control of communicable diseases is fast changing with advances in knowledge of their transmission. Quarantine, previously emphasized, has become less important. Quarantine has been shown to be of little real value in the control of diseases of high contact communicability (measles, chicken pox, smallpox). It is of little significance in those diseases in which the spread of infection is less direct (meningococcus disease, streptococcosis, poliomyelitis, typhoid, diphtheria) where the agency of transmission involves subclinical infection and the carrier state and when isolation is imposed only upon the obviously ill. Isolation of the patient is even less of value in the control of insect-borne viruses and rickettsiae (encephalitis, typhus, Q fever).

The origin of communicable disease hospitals was the pest house, which was for the segregation of the ill from the well and not for the protection of patients from one another. The newly developed concept is for individual isolation consistent with the methods of transmission and the development of aseptic nursing by which the patient may be appropriately isolated almost anywhere, except that those diseases of extremely high contact communicability (measles, etc.) can scarcely be controlled by any manner of precaution.

The communicable disease hospital has developed away from the pest house and now exists best as a fever hospital where transmission is controlled by precautions on the part of the personnel and where the emphasis is upon superior facilities for therapy rather than enforcement of absolute quarantine. The problem of communicable disease has become identified with the general problem of infectious disease.

Read as part of Panel Discussion on What's New In Pediatrics at the 77th Annual Session of the California Medical Association in San Francisco, April 11-14, 1948.

The public has been indoctrinated in the employment of precautionary measures with resultant avoidance of many common infections during childhood. This has resulted in spreading childhood infections over a larger period of the life span and has led to some curious effects from the occurrence of these diseases in adult years. It has been seriously proposed that under primitive conditions exposure to the virus of poliomyelitis occurred commonly in infancy at a time when resultant disease was silent or non-paralytic and that better protection has caused this disease to assume epidemic proportions in older age groups with paralytic sequellae.

German measles is traditionally a childhood disease of no great significance. Its increased occurrence in older age groups has provided the evidence of its dismal effects on the fetus when it occurs early in pregnancy. This disease is more benign at an early age.

Newer methods of therapy have greatly modified the course of many infections. Antibiotic therapy and chemotherapy have caused the treatment of infections due to the streptococcus, meningococcus, pneumococcus, and other organisms to be greatly improved and simplified. Meanwhile latent effects of antigen stimulation have become recognized as important in the production of late sequellae. This applies strongly to streptococcal diseases in which rheumatic sequellae are seen long after the stage of acute pyogenic infection and is doubtless significant in many other infections, possibly serving to explain some of the late complications of virus infections such as the encephalitides which complicate the exanthemata.

Certain infections have been little influenced by new methods of therapy. Diphtheria is demonstrably best controlled by immunization and best treated by antitoxin. Warnings of increased incidence point mostly to greater morbidity and mortality in older

age groups past the effect of immunization. The actual value of sulfonamides and antibiotics has not been acceptably proved even in the carrier state.

Scarlet fever is rapidly coming to be regarded as only a part of the general problem of streptoccal disease in which the eruption does not notably indicate increased communicability. Immunization has not encouraged general acceptance; serums which are potent against the erythrogenic toxin are little used and treatment seems best served by penicillin and sulfonamides.

In measles unmodified human serum for prophylaxis has encountered the newly recognized risk of homologous serum hepatitis which is inherent in all such preparations. Gamma globulin affords better protection without this danger. It has become apparent that modified measles does not unfailingly protect against future exposure and I believe that it is not certain that modified measles is exempt from post-measles encephalopathy. The prophylactic value of penicillin and sulfonamides against secondary invaders in measles is uncertain and probably unjustified.

Meningococcus disease is amenable to therapy with sulfonamides, which is the agent of choice far above former therapeutic measures.

Whooping cough has shown an overall increased incidence although most of us can point to diminution to the vanishing point in practices in which patients are 100 per cent immunized. Statistical evidence of the value of immunization will be affected only by early universal vaccination in which lowered exposure rates will augment the effect of varying degrees of immunity.

Poliomyelitis is not susceptible to any of the new antibacterial agents for prophylaxis or treatment, perhaps because this minute virus has little in common with the life processes of larger viruses and bacteria. This problem demands a new and imaginative approach not comprehended in our philosophy. The epidemiology of poliomyelitis indicates the absence of a sequence of exposure, incubation period, disease and immunity comparable to better understood infections. Host susceptibility is quite as important a factor as the study of the virus itself.

The arthropod-borne viruses of the encephalitides have assumed increasing importance and, although knowledge of the vectors and their control has increased, little has been added to specific therapy.

To the problem of influenza has been applied the mass administration of virus vaccines. Failures of protection have been encountered with respect to certain strains. This poses a neat problem in the selection of strains for future vaccination, especially against such a pandemic as occurred 30 years ago. The propriety of the use of influenza vaccines in the private practice of pediatrics seems dubious to me in view of their uncertain action, the short period of potential protection and the possibility of egg protein sensitization.

Rickettsial infections have assumed increasing importance. Typhus and kindred infections have been encountered throughout the United States. Rickettsial pox was identified in apartment houses in New York City—of all places! The year's prize for interesting medical writing would be awarded by me to *The New Yorker* for its account of this disease. Q fever, which couldn't happen here, did—in Texas and in California. The study of the vector problem in these diseases is of great magnitude. It may certainly be suspected that many disease problems of this nature await only a deft and inquisitive approach.

The use of paraminobenzoic acid in the therapy of certain rickettsial diseases has provided us with an entirely new therapeutic approach in which interference with the enzyme systems upon which the life processes of these organisms depend is a principle which may be susceptible to much further extension.

The recent studies on histoplasmosis indicate that a widespread form of infection simply awaited study and recognition; and the increasing frequency with which toxoplasmosis has been recognized, often in early infancy, indicates the probability that latent infection of this nature may be far more common than we suspect.

384 Post Street.

QUESTIONS AND ANSWERS

Question: When do you advise the use of immune globulin in measles prevention? (Prevention referring both to complete protection and modification with a comment on dosage.)

DR. SHAW: This question might provoke a general discussion with some differences of opinion. My own practice is not to use globulin at all under six months of age and to use it sparingly between six months and one year. Usually until the age of six months the infant has a certain amount of residual immunity which is either transplacental specific immunity or consists of a relative insusceptibility to this infection at this age and this factor suffices to protect to a variable degree during the second six months. From one to three years of age I usually employ gamma globulin in an effort to produce modification in a child who is otherwise healthy. 0.025 to 0.02 cc. of gamma globulin per pound of body weight given on the day of appearance of the rash in the child to which the patient has been exposed will pretty reliably result in mild modified measles. There are some individual differences in susceptibility, and the intensity of exposure is another factor which affects the success of the procedure. It is impossible to predict the exact results and sometimes this dosage fails to protect and occasionally results in complete protection rather than modification. The exact degree of permanent protection which is conferred by a modified attack of measles is also variable and is somewhat dependent upon the degree of symptoms—the more evidence of disease which is present, the more likelihood there is of enduring immunity.

In the age period of over three to perhaps four years of age I am sufficiently old-fashioned simply to permit the child to go ahead and have measles and thus develop permanent protection. In the presence of other infections and in the convalescent stage of other respiratory infections, doses somewhat in excess of the above should routinely be employed for complete protection against the present exposure.

Question: Is immune globulin of definite value in the treatment of measles after the rash erupts, particularly in children under the age of two years, and if so, what dose do you use?

DR. SHAW: I think this is a most important question. We have just had a patient who was admitted to the hospital with rather severe scarlet fever, and on the eighth day after admission he developed measles—we at least had the assurance that he was not exposed in the hospital. This child was given 10 cc. of gamma globulin, which corresponds to about 250 cc. of immune serum, and he proceeded to have a very mild attack of measles which I think was definitely the result of the gamma globulin administration. I believe there are many times when this principle of treatment should be employed. Toomey has shown that if sufficiently large amounts of convalescent serum (or globulin) are given during the early stage of measles, considerable modification can be effected even if this is done only a short time before the rash appears. This procedure is most useful when symptoms of measles appear during the course of another infection or in the surgical patient or at any time in which full-blown measles is most disadvantageous. I think this is an interesting contradiction of the statement by Rivers that in virus diseases nothing can be accomplished, once symptoms are evident (Rivers happened to be talking about the serum therapy of poliomyelitis), to modify the course of such a disease because of the intracellular habitat of the virus. Under these circumstances, measles can be modified if sufficient amounts of an immune serum principle are employed and I have seen the same thing happen more or less inadvertently in the course of chicken-pox in which transfusions were administered just as the very first eruption appeared. In these cases the first few vesicles appeared and following the transfusion these vesicles rapidly regressed and practically no other eruption was evident.

Question: Why has the use of immune globulin eliminated the danger of serum hepatitis?

DR. SHAW: I don't know—except that while the virus is potentially present in the whole serum it may be eliminated by the processing which results in purified gamma globulin. Furthermore there is some concentration of antibodies against the hepatitis virus in pooled gamma globulin preparations. Even in pooled serum preparations in which processing has not eliminated the virus of hepatitis the coincident presence of antibodies against the hepatitis virus may be the factor which results in inhibiting the appearance of symptoms for such a long time after the whole serum is administered. There was a publication during the past week which you have doubtless all seen, pointing to the fact that the presence of virus and immune substance in the same preparation was sometimes responsible for a long incubation period. This same phenomenon is sometimes seen in measles prophylaxis in which very small doses of immune serum or globulin are given, under which circumstances measles may appear after a prolonged incubation period instead of complete protection. Conceivably if a pooled specimen of serum or plasma contains small amounts of the virus of hepatitis as well as small amounts of antibody, homologous serum hepatitis may follow after an incubation period of 90 to 120 days.

Question: Inasmuch as it is difficult to tell when a child will be exposed to measles, how about exposing him deliberately and then giving immune serum globulin to modify the attack?

DR. SHAW: I would not do this. I am not sufficiently hardy to expose a child definitely to measles and thus take the responsibility for whatever might occur and I am not confident that the dosage of gamma globulin could unfailingly be selected so as to provide the child on the one hand with minimal measles and on the other hand with permanent immunity. Many of the patients who have had modified measles in childhood secured through the use of gamma globulin after exposure have only a transient succeeding immunity and later on may be completely susceptible to the disease. I am afraid that many of those whom we have thus protected in childhood will be fully susceptible in adult years. We may see many curious things with a lot of pediatrics relegated to adult medicine in later years.

What's New in the Field of Immunization

JOHN J. MILLER, JR., M.D., *San Francisco*

IN the field of immunization there have been a number of recent developments which are worthy of discussion. Mumps can be added to the list of diseases which in the future may be prevented. The studies of Stokes, Enders, and their associates[27,5] are encouraging. In experiments, formolized mumps virus from monkey parotid glands protected about 50 per cent of children against infection. Attenuated virus from egg passage may eventually prove to be the answer.

The somewhat precarious status of two older immunization procedures has been altered in the past year. The outlook for successful immunization against influenza has become less promising. Contrary to earlier studies made in United States Army camps, three field trials reported during the past year yielded no evidence of protection.[6,30,26] These failures are in the main accounted for by the appearance of new strains of virus antigenically distinct from those incorporated in commercial vaccines. Unfortunately, there is also reason to believe that new strains will continue to appear. As the immunity conferred is apparently almost strain-specific, vaccines in the future either must be highly polyvalent or broadly antigenic, or may even have to be produced rapidly in the face of a spreading epidemic after the infecting strain has been isolated. The one cheerful aspect of the present status of vaccination against influenza is the likelihood that calcium phosphate adsorbed vaccine[25] will produce a firmer and more lasting immunity than do the currently available unadsorbed products.

The controversial status of BCG vaccination against tuberculosis, on the other hand, seems to be resolving. Recent reports from the Indian reservation,[1] from Denmark,[12] and from Chicago,[22] have demonstrated that decreased morbidity and mortality rates can be obtained with some preparations of vaccine. The evidence has been considered sufficiently valid by the United States Public Health authorities to lead them to commence further field studies and to attempt laboratory standardization of the vaccine.[29] The Surgeon General's office, however, does not feel that BCG vaccine should be made commercially available at present. Public health officials desiring to set up controlled studies should contact the office of the Tuberculosis Control Division of the U. S. Public Health Service and obtain vaccine through this channel.

Now, a word about the oldest immunization procedure. There is widespread and misplaced confidence in the validity of the "immune reaction" to cowpox vaccine. It has long been known[4] that local erythema and induration appearing in 24 hours may result from inoculation with dead virus in an individual allergic to calf lymph. Nevertheless, the occurrence of smallpox in American and British soldiers with records of recent "immune reactions" has jolted our complacency.[4] Leake in the U. S. Public Health Service handbook on vaccination[16] describes the "early reaction" as one in which "the broadest redness is reached in 8 to 72 hours after vaccination." There is "a slight elevation of the skin . . . and usually no vesicle." He then goes on to state that "such a reaction should not be called a reaction of immunity unless fully potent vaccine has been used." But how are we to know our vaccine is fully potent? The only answer is: By observing instances of primary local vaccinia following inoculation with the same lot of vaccine at about the same time. The best that we can do, then, is to obtain new lots of vaccine frequently and always keep them in the freezing chamber of a refrigerator.

In diphtheria immunization there are still problems—that of the susceptible adult and that of the individual who is sensitive to the toxoid. Commonly these two problems coexist. Toxoid sensitivity tests are essential before toxoid is given to adolescents and to adults. It is possible that the sublingual application of toxoid tablets[2,20] will in the future prove of value in reimmunizing the toxoid-sensitive adult.

In the field of pertussis immunization there has been no substantial contribution since Sako and his coworkers[24,23] showed that infants under three months of age could be actively immunized. The question of whether precipitated vaccine is necessary for immunization at this age has not been settled.

Active immunization against tetanus has such a splendid war record that unwarranted statements have appeared in the literature. It has been said that when a previously actively immunized individual is wounded, all one need do is to give him a "booster" of tetanus toxoid. This complete confidence in primary immunization and in the secondary anamestic response requires a dash of cold water, in my opinion. The very great protection against tetanus obtained by the armed forces was in men very recently immunized. The majority of troops also had had routine annual "booster" reinjections.

The effect of the lapse of time on the speed of the response to reinjection of toxoid is not well known. Contrary to the reports of others,[21,19] we have observed that with the passage of time the speed of response is decreased. In some individuals, after an interval of five years or more since the last previous injection there may be no detectable antitoxin seven days after the reinjection. Furthermore we have observed that children basically immunized with pre-

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cipitated or adsorbed toxoid respond to a "booster" faster than do those basically immunized with fluid toxoid. Thirdly, and on the other hand, fluid toxoid produces a more rapid increase in antitoxin than does precipitated toxoid in children basically immunized with the latter. In other words the immunization mechanism is sensitized better by a slowly absorbed antigen but is stimulated faster by a rapidly absorbed antigen.

One may ask, "Are these measurements of antitoxin significant?" I believe so, for the following reasons. Let us examine the few cases of tetanus that did occur in immunized soldiers during the recent war. A total of 28 cases have been reported from the British and American armies.[3,17] All cases occurred after severe wounding, and almost all occurred after unusually short incubation periods—the shortest was two days. The fatality rate in these few cases was surprisingly high, 50 per cent. Apparently what occurred was that active immunization prevented tetanus in everyone except those suffering from massive intoxication following severe wounding. Here the incubation period was too short for a booster to stimulate antitoxin production. When the British gave prophylactic antitoxin in such cases, they obtained a lower fatality rate than we did with toxoid "boosters."

If both antitoxin and toxoid could be administered in such severe cases, would both immediate and delayed protection result? From evidence obtained in our laboratory, I believe so. Studies following the simultaneous administration of antitoxin and toxoid in different extremities of previously immunized animals indicate that the secondary immune response, unlike the primary immune response, is not prevented by circulating heterologous antitoxin. In summary, then, it would appear that maximal protection against tetanus can best be obtained by (a) inducing basic immunity with precipitated toxoids, (b) maintaining high levels of antitoxin with routine biennial reinjections of precipitated toxoids, and (c) employing rapidly absorbed fluid toxoid when wounding occurs. In cases of compound fractures or other wounds likely to be massively contaminated, or in cases in which the interval since the last toxoid injection is five years or more, prophylactic antitoxin should probably be administered in addition to the booster at the time of wounding.

In regard to passive immunization procedures, what's new, of course, is gamma globulin. In addition to being highly effective, and the agent of choice, in the prevention of measles, it has been employed in three other virus diseases. In mumps it is apparently not effective unless prepared from mumps convalescent serum,[8] which is not commercially available. On the other hand, ordinary gamma globulin from normal adult serum has been reported to confer protection against chickenpox.[7] Should this be confirmed, we will have a very useful agent in protecting sick infants and children exposed in hospitals.

In epidemic and endemic viral hepatitis ordinary gamma globulin is effective if administered during the first two weeks after exposure. Its great value was clearly demonstrated in two institutional epidemics[2,8,11] and in a large epidemic among our troops in Italy.[9] The dose for children is 0.22 cc. per kg. of body weight.

The importance of preventing the spread of epidemic hepatitis in troops at war or in children in an institution is obvious. But should we attempt to protect the child who has been exposed at home or in school? An attack of viral hepatitis produces immunity which is not strain-specific.[10] On the other hand, there is now ample evidence[15] that this disease is not always benign. Fatal cases are extremely rare but permanent liver damage may result.[18] Repeated needling of the liver for biopsy specimens is reported to have shown transition from acute hepatitis to cirrhosis in a few instances.[14] Fortunately for pediatricians, chronic liver disease following hepatitis is far more common in adults than in children.[13] Nevertheless we have recently observed a case of portal cirrhosis in a 12-year-old boy who had had an attack of typical catarrhal jaundice nine months previously. No other possible contributory factor was found. It is my opinion that although the dangers of infectious hepatitis are remote in childhood, this preventable disease should be prevented by passive immunization whenever possible.

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QUESTIONS AND ANSWERS

Question: Why not three doses of toxoid for basic immunity?

DR. MILLER: There is evidence that basic courses of three injections of precipitated tetanus toxoid induce higher and more enduring titers of antitoxin than do courses of two injections.

Question: Is not a recall injection of toxoid preferable to antitoxin?

DR. MILLER: Yes, indeed, for thereby sensitization to horse serum is avoided. A recall injection of toxoid can be relied upon and should be employed in previously immunized individuals for all puncture wounds and common lacerations. As I have already stated, antitoxin need be considered only in cases of compound fractures, massively contaminated wounds, shock (in which the immune response may be impaired), and when the interval since the last injection of toxoid is five years or more. Under these conditions I believe antitoxin should be administered in addition to toxoid. The antitoxin will afford immediate passive protection against short incubation period tetanus while the patient's immune mechanism is mobilizing his own antitoxin.

Question (Moderator): How much antitoxin, Dr. Miller?

DR. MILLER: Five thousand units if the patient is in shock, or severely wounded. Fifteen hundred units if the time interval since the last injection of toxoid is five years or more and the wound is not severe.

Experimental Use of Testosterone Compounds in Premature Infants

E. Kost Shelton, M.D., and Jerome S. Mark, M.D., *Los Angeles*

PREVIOUS laboratory investigations have indicated that the premature infant has many metabolic defects. In particular there are inadequacies in nitrogen, calcium, and phosphorus storage; faulty ability to absorb fat; and multiple requisites conditioned by the rapid rate of growth. Since nitrogen storage and utilization are in part the physiological effects desired, it occurred to us that testosterone, one of the most important metabolizers of nitrogen, might be a rational drug to employ as an adjunct in the care of certain premature infants.[3]

During the past year infants of both sexes on the premature wards of the Los Angeles County General Hospital received various testosterone compounds and the effects were observed. The materials considered suitable for such a study were the methyl derivatives for oral use, and the propionate derivatives for intramuscular administration. Methyl testosterone is obtainable in tablet form which can be crushed and introduced directly into the formula, or as a propylene glycol solution which may be dropped directly under the tongue. Without precedent the dose of methyl testosterone was arbitrarily set at 5 mg. daily. It was found that the propylene glycol solution lent itself more readily to administration. Testosterone propionate was given intramuscularly in 4 mg. doses daily. Treatment in both series was begun at 12 hours after birth and continued for three weeks.

The infants observed weighed under 2000 grams and for each group there was a similar group of the same age and weight, under the same general care, as control. Daily observations were made of the weight, alertness, type of stool, amount of lanugo, size of clitoris and penis, and the number of erections. These, in addition to the length of time required to regain the birth weight, and that required to gain to 2500 grams in body weight were used as the ultimate basis for evaluation.

To date there has been a total of 74 patients which have been under observation for a year. These infants, of both sexes, to which both types of testosterone compounds were given, have been divided into two groups, those weighing between 1000 and 1500 grams and those between 1500 and 2000 grams at birth. A significant indication of the benefits obtained by the use of both testosterone compounds was evident by the enhanced welfare of the treated prematures in both weight classifications. In the 1000 to 1500 gram weight groups an average of 14.7 days was required by the untreated controls to regain their birth weight. Those on methyl testosterone in the same weight group required an average of 9.0 days; and those on testosterone propionate only 7.5 days. Thus comparison between the treated and the control group reveals a 50 per cent reduction in the time required to regain birth weight. Similar results were obtained in the 1500 to 2000 gram group. It was also found that whereas the controls required 42 days to gain to 2500 grams, those to whom the propionate was administered required only 35 days and those receiving the methyl compound only 32 days to reach this same level. Again these treated prematures revealed a significantly earlier attainment of maturity when compared with their untreated controls.

An even better indication of the benefits derived from the use of testosterone compounds was obtained from the study of four sets of twins. Here the larger of the two, the one with the greater chance for survival, was used as the control while the smaller was given testosterone. All of the twins on the testosterone compounds, who theoretically should have taken longer to regain their birth weight, did so in a much shorter period than their larger more mature control siblings. In fact, in three of the four sets, the birth weight was maintained from the onset of treatment while in the fourth there was an approximate 50 per cent reduction in the anticipated number of days required to regain the birth weight. Here again the days required to gain to 2500 grams showed a reduction in the twin treated with testosterone in three out of the four, while in the fourth set only two days longer was required to bring the smaller infant to maturity.

It is now generally accepted that testosterone compounds cause a decline in urinary nitrogen reflected in the urea fraction, unaccompanied by an increase in the plasma protein, non-protein nitrogen, or hemoglobin concentrations.[1] As there is no change in the amount of fecal nitrogen, it is evident that this retention of nitrogen must have some tissue-building significance. There is also a decline in urinary sodium, associated with a somewhat smaller decline in urinary chloride, a decline in urinary potassium and in total urinary volume. The evident end result of this is in water retention and a general protein anabolism, noticeable in the genital tissue, but more objectivized in the soma, with resultant increased growth and muscle hypertrophy.

In other clinical experiments it has been found that testosterone propionate and methyl testosterone exercised similar effects.[5] The only exception appeared to be that some observers found that methyl testos-

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From the University of Southern California Medical School and the Los Angeles County General Hospital.

terone tended to promote hypercreatinuria whereas propionate decreased it.[4] It is now felt that the fundamental effects are the same. The apparent discrepancy in creatine metabolism is merely ascribable to the fact that in the case of methyl testosterone administration the nitrogen retention is so profound as to cause a spilling over of creatine. In comparing the clinical effects of methyl testosterone with the testosterone propionate, no significant differences could be observed in the prematures in our series. The intramuscular administration perhaps did offer advantages over the oral route in accuracy of dosage, but the ease of administration of methyl testosterone in propylene glycol and the freedom from the infection hazard are perhaps more worthy of consideration.

Daily observations for any of the previously mentioned signs of virilism revealed no significant difference between the groups. Our follow-up examinations during the first year continued to support these findings. Following prolonged and injudicious treatment with testosterone in some adolescent and adult females a lowering of the voice has been found.[2] We watched for such an untoward effect in the infants both during the administration period and throughout the first year following treatment but no abnormalities in cry could be detected. Roentgenograms of the long bones were taken at the beginning of the series and repeated at the end of the year. There was no difference in bone age between the controls and the treated infants, but in general all infants showed that slight delay in osseous development characteristic of prematures.

SUMMARY

Seventy-four premature infants, of both sexes, weighing under 2000 grams at birth were given either oral methyl testosterone 5 mg. daily, or testosterone propionate 4 mg. daily parenterally. A similar untreated group was observed as controls. A distinct shortening in the time required to regain birth weight and in the time required to gain to 2500 grams was noted in both treated groups. In four sets of twins the smaller, treated infant showed increased somatic development over its larger untreated control sibling. No contraindications to the use of testosterone compounds were observed.

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QUESTIONS AND ANSWERS

Question: What about mortality rates of treated and untreated prematures?

DR. MARK: In our preliminary series we have not found any statistically significant differences between the mortality rates of the treated and the untreated premature infants. This is understandable as our treatment was begun at the end of 24 hours and it is during this time that the greatest mortality occurs in premature infants. However, Varden, who has done similar work in a San Bernardino hospital with premature infants, reports a lower mortality rate in those individuals treated.

Question: Regarding testosterone, and the interval you use—three weeks—have you any information on other intervals that might be used, and any information on catheterizations or prolonged administration?

DR. MARK: In this, the first series we have ever attempted, three weeks was chosen arbitrarily. It was believed that during this time a maximum physiological effect could be obtained with no possibility of any adverse effects due to prolonged treatment. Our follow-up study at the end of the first year supports this view. Experimental work shows that up to eight months of treatment with high doses has no effect on the epiphyseal centers.

Some Diagnostic and Therapeutic Techniques in Cystic Fibrosis of the Pancreas

GORDON E. GIBBS, Ph.D., M.D., *San Francisco*

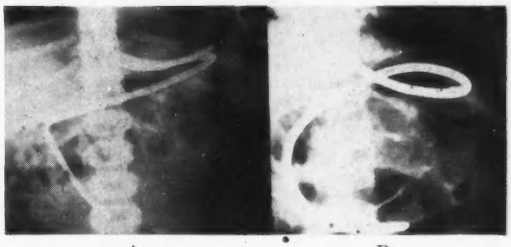
THE frequency of cystic fibrosis of the pancreas was appreciated only as recently as 1938.[2] The incidence has been estimated to be 1.7 per 1000 live births in New York City.[3] With the advent of penicillin some improvement in the prognosis has occurred.[11] Differentiation between cystic fibrosis of the pancreas and the various other entities of the celiac syndrome is often difficult, while the confidence resulting from a definite diagnosis favors adequate pursuance of the appropriate therapies.

The typical case of the fibrocystic disease is in an infant or child with history of chronic cough; soft, foul, bulky stools; retarded weight gain and growth, enlarged abdomen, poor musculature, and perhaps x-ray evidence of pulmonary inflammation and fibrosis. Microscopic examination of the stool for excess fat by sudan stain is a technique available to any office and is of great usefulness as a rough measure to aid in recognition of the celiac syndrome.[4]

In diagnosis of cystic fibrosis of the pancreas most reliance has been placed on the absence of trypsin from the duodenal fluid. In adults the most adequate technique of duodenal drainage has utilized the bi-lumen, gastro-duodenal tube. The gastric lumen permits withdrawal of the gastric fluid so that it does not contaminate the duodenal specimen. The need for such a technique, but the lack of successful application of it to infants, has been indicated by Andersen.[1]

In the present studies an attempt has been made to fill this need. Before a small double-lumen tube was devised, double drainage was accomplished by means of two separate tubes, one through each nostril (or one or both through the mouth in infants without teeth). Two tubes in place are shown in Figure 1A. This procedure was used in 30 tests and seemed to accomplish the objective of minimizing contamination of the duodenal sample by gastric contents. The duodenal tube was of 12 (French) diameter and had a gold tip. A 10 F or 12 F tube was used for the gastric drainage. The difficulties seemed to be due to the tendency of the two tubes to adhere so that introduction of the gastric tube after placement of the duodenal was somewhat more uncomfortable to the child, sometimes resulting in regurgitation of the duodenal tube into the stomach. Any separate adjustment of the tubes was difficult but the technique was usable and is desirable if a small bi-lumen tube is not available.

Figure 1B shows a bi-lumen tube, use of which has been apparently successful and thoroughly convenient in 31 attempts in patients ranging down to newborn size. This tubing also has 12 F outside diameter and is 120 cm. long.* It has two equal lumina, semicircular in cross section side by side. A gold tip of the same diameter (4 mm.) 15 mm. length, and 2.7 gm. weight is attached to the bottom.† Holes for the duodenal juice are immediately above this.



A B

Figure 1.—(A) X-ray showing two separate single-lumen tubes in place for separate drainage of gastric and duodenal fluids in a three-year-old child. (B) X-ray showing a bilumen tube in a 10-month-old infant. The duodenal tubes in the two films are of the same outside diameter (12 French).

Seventeen cm. higher, in the other lumen, are holes for gastric juice. This lumen is blocked below the gastric holes by a metal plug. Stubs of 15 gauge needles are tied into the upper end, through which aspiration is made alternately with syringes.

Entry of the tube into the duodenum is facilitated by placing the child on the right side. Directed by the weight of the tip, the lower perforations reach the pool of fluid in the pyloric corner of the stomach, as indicated by a steady drip or easy aspiration of fluid. Water is injected to maintain such a pool until the appearance of yellow juice usually heralds the passage of the tube into the duodenum. When clear, alkaline, yellow fluid is obtained from the lower lumen, while acid, turbid, white fluid comes simultaneously from the gastric, there can be little doubt that the tube is properly placed even without fluoroscopic verification, although the latter has always been used in the present study. In some cases, particularly in pancreatic deficiency, no duodenal fluid was obtained at first, and only at fluoroscopy was the tube discovered to be in the duodenum.

A good quantitative trypsin method is essential. In several debilitated infants without specific pancreatic deficiency the trypsin concentration was so low as to be undetectable by inexact office procedures, but high enough to rule out a typical case of cystic fibrosis of the pancreas.

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* The rubber tubing was made through the courtesy of Mr. Emil Davidson, Clay-Adams Company, New York City.

† The gold tip was made through the courtesy of Dr. W. A. Elsasser and Dr. W. L. Wylie, University of California College of Dentistry.

Values of 58 x 10^{-4} units of trypsin, 15 x 10^{-4} units lipase and 83 x 10^{-3} units amylase per cc. were obtained in the control child of whom the vitamin A curves are shown in Figure 2. This was a well-nourished two-year-old boy with occasional rectal prolapse. The infant in Figure 2 with pancreatic deficiency had zero values for trypsin, lipase and amylase. This infant had meconium ileus in the newborn period. She later developed a chronic cough. The duodenal drainage was done at the age of 8 weeks. (At this age a normal infant also shows no amylase.) The child representing celiac disease was 27 months old and had enzyme values of 21 x 10^{-4} U trypsin, 19 x 10^{-4} U lipase and 59 x 10^{-3} U amylase.

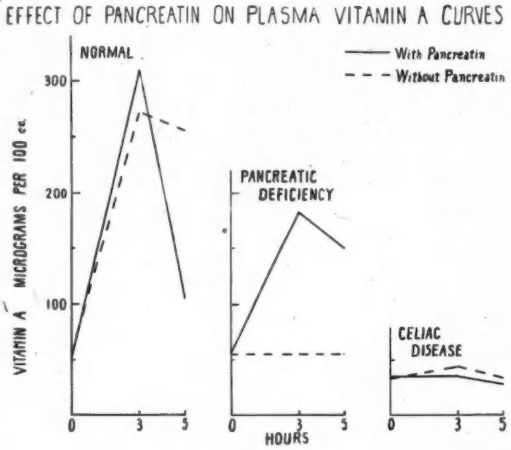

Figure 2

The rise in plasma vitamin A concentration which normally follows an oral test dose of vitamin A ester in fish oil does not appear in the celiac syndrome. Administration of pancreatin tends to correct the curve in pancreatic deficiency.[10] Curves from an infant with cystic fibrosis of the pancreas are presented in Figure 2. In this illustration the lack of effect of pancreatin on the normal curve of a normal child and on the flat curve of a child with celiac disease is also shown. These curves approximate the average obtained in 17 cases of cystic fibrosis of the pancreas, 10 cases of non-pancreatic celiac syndrome, and 12 controls. Use of this effect as a diagnostic measure has seemed a helpful adjunct to duodenal drainage. Its reliability is being further investigated.

Meanwhile the therapeutic implications of the effect deserve emphasis. The rise in vitamin A serves as an index of the effectiveness of pancreatin in restoring not only the digestion of vitamin A ester, but probably also of other foodstuffs. Inability to digest vitamin A ester may be circumvented by use of vitamin A alcohol.[10] Similarly, amino acids may be used to replace protein.[14] Prolonged use of an artificially hydrolysed, complete diet would, however, be difficult. The present data contribute to the assurance that relatively normal digestion can be achieved by the simple and practical expedient of adequate pancreatin therapy.[7] Corresponding data concerning the effect of pancreatin in protein digestion as indicated by blood amino acid concentrations has been presented by other workers.[16]

Dosage of 0.3 to 1.5 gm. of enteric-coated pancreatin granules following each meal has been used for routine therapy in the present series. 0.15 gm. pancreatin for each kg. body weight and 7000 units kg. vitamin A as halibut liver oil have been the test doses for the vitamin A curves. The tests were started before breakfast or the early morning formula and other vitamin concentrates were withheld.

Vitamin A curves with pancreatin in patients with pancreatic deficiency are also useful for comparison of the effectiveness of different pancreatin preparations and dosages.

Vitamin A has been determined by the Carr-Price reaction,[12§] pending acquisition of equipment for use of a capillary-blood method.[8]

In view of the fact that vitamin A levels of the plasma are depressed in both infection and impaired intestinal processes, determination of fasting vitamin A is of unique value in the follow-up of these cases.[13] In view of the possible effect of vitamin A deficiency to aggravate the pulmonary disease it seems advisable to keep the fasting vitamin A level within or above the normal range. This can be accomplished by high vitamin A dosage, pancreatin and antibiotics. We are using 15,000 to 50,000 USP units of vitamin A daily in most patients. As other indications of the status of the patients, the weight gain, leukocyte count, the penicillin sensitivity of the pulmonary flora and the interval history concerning cough, fever, and stools are also significant.

PENICILLIN AEROSOL

The terminal development in cystic fibrosis of the pancreas has been pulmonary infection. Benefit from use of penicillin has been dramatic. It seems obvious, however, that the best possible nutritional state, as maintained by vitamin A, pancreatin, etc., would

The studies here reported were done by the method of Anson, in which tyrosine from a hemoglobin substrate is determined with use of a photoelectric colorimeter.[5] The hemoglobin was prepared by dialysis of human over-age bank-blood. The more recent method using sulfanilamide azoprotein would probably also be satisfactory.[9] Amylase was determined by the volumetric hypoiodite method of Willstatter.[11] Lipase was determined by titration of the fatty acids liberated from 1.2 millimols benzyl butyrate in a bile-glycerol mixture.[6] One lipase unit liberates one milliequivalent of fatty acid per minute. Units are otherwise as defined in the references except that all digestions were done at 37.5°C. These three determinations could be completed within an hour. The tubes of juice were kept in an ice bath during collection and frozen if not immediately analyzed.‡

‡ I am indebted to Dr. I. L. Chaikoff and Dr. S. Chernick, Division of Physiology, University of California, for suggestions concerning the enzyme methods.

§ The method was standardized by use of the USP Vitamin A Reference Standard distributed by the Board of Trustees of the United States Pharmacopoeial Convention, 4738 Kingsessing Avenue, Philadelphia 43, Pa.

Figure 3.—Various equipment for penicillin aerosol administration.

be prerequisite to maximal success in penicillin therapy. Low fat diet and postural drainage are probably also of benefit.

The danger in patients receiving penicillin is the appearance of penicillin-resistant organisms. Such an outcome is believed to be facilitated by inadequate penicillin therapy. In our present program the periods (usually one to two weeks) of penicillin (25,000 to 50,000 units four times daily) alternate with periods without penicillin of a duration depending on the time of return of increased cough. Sulfonamides are usually used in prophylactic oral dosage during the periods when penicillin is not given. On the hospital ward, penicillin is given intramuscularly along with the aerosol inhalation. The program of use of aerosol alone represents a compromise with expediency which is practical in the home.

Some of the various arrangements for penicillin inhalation are illustrated in Figure 3. The oronasal B. L. B. mask is shown on the child.* The assemblies on the other side of the picture are alternative equipment. The box is for small infants. Some patients use oxygen tanks at home. Others have inexpensive automobile foot-pumps as illustrated. The foot-pump is especially satisfactory in case of a ten-year-old boy who coordinates his inhalations with strokes of the pump, and holds the nebulizer directly in his mouth. When a foot-pump is used it is advisable to insert a wad of gauze somewhere in the air line to catch any trace of oil, and the gauze should be changed from time to time. Difficulty has been encountered of some nebulizers being ineffectively constructed. Sometimes plugging of the small jet also occurs. Nebulizers must be tested occasionally by being held up to the light during use, for observation of the mist.

Twenty cases of cystic fibrosis of the pancreas have been studied at the University of California Hospital in the past year. Repeated weight records of 14 of the patients on essentially the regime recommended previously in this presentation, are at hand. Nine of the 14 have gained weight at a rate greater than the normal average for the age. Four others have also gained weight, but at a rate somewhat slower than the average. One, who was first seen after advanced pulmonary changes, lost weight over a six month period, was found to have a penicillin-resistant organism, responded poorly to streptomycin, and died.

* Size 4 B has been used, but is no longer available. We plan to use size 5 C instead. Mask and nebulizer assemblies are available through the University of California Pharmacy.

SUMMARY

Construction and use of a double-lumen gastroduodenal tube for duodenal drainage in infants is described.

The effect of pancreatin to raise the plasma vitamin A tolerance curve in pancreatic deficiency is illustrated and its therapeutic significance emphasized.

Equipment for administration of penicillin aerosol is illustrated and discussed.

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QUESTIONS AND ANSWERS

Question: Has any child with cystic fibrosis and lung changes ever reached puberty?

DR. GIBBS: The oldest child that we have is ten years old, and judging by the way he is doing now, he should reach puberty. The oldest among Andersen's reported cases was 14½ years. I believe that there is a degree of mildness in cases, and we are at present investigating the probability that some fibrocystics may be mild enough so that they have survived into adulthood, although so far this has not been demonstrated.

Question: You stated the incidence of pancreatic fibrosis as being 1.7 per thousand. That seems a surprisingly high incidence to most of us. The question is: Does that not mean that a great many cases are being missed?

DR. GIBBS: That is Dorothy Andersen's figure for New York City; we will have to take her word for it. This estimate seems more and more reasonable in view of the increasing number of cases that are being proven here—cases that in the past would have been fatal with some indefinite diagnosis.

MODERATOR: What is the adequate dosage of pancreatin?

DR. GIBBS: We are feeling our way in that; it depends on the type of pancreatin that is used. The dosage that I am using therapeutically ranges from 0.3 to 1.5 grams of enteric-coated pancreatin granules after each meal. As judged by the effect on the vitamin A absorption curve, plain pancreatin should be given in twice the dosage.

Question: Have you employed liver extract and vitamin B parenterally to raise vitamin A absorption? (2) Have you performed the amino acid absorption curve as a substitute for duodenal assay as in New York City?

DR. GIBBS: We use liver and vitamin B in celiac disease, and it seems very effective in certain cases. I doubt whether the amino acid absorption test is as reliable as duodenal assay. I have not used the amino acid test myself, but I mentioned the work of West and Wilson at Ann Arbor. They have, incidentally, obtained for amino acids essentially the same difference in curves with and without pancreatin, as I showed here for vitamin A. They determined the amino acids liberated from casein or gelatin.

Question: Does B_1 and liver injection still play an important part in the treatment of fibrocystic disease of pancreas?

DR. GIBBS: That is an idea that should be played with. True celiac disease may be a sort of vitamin deficiency, something related to the vitamin B group, and it may possibly be precipitated by various types of intestinal disturbances including cystic fibrosis of the pancreas. I am waiting for a case of fibrocystic disease in which the nutrition and diarrhea do not respond to pancreatin, and will respond to vitamin B and liver, but have not found one yet.

Important Factors in the Diagnosis of Patent Ductus Arteriosus

SAUL J. ROBINSON, M.D., *San Francisco*

WITH the advent of a highly successful surgical procedure to eliminate patent ductus arteriosus, diagnosis of the condition assumes more than academic importance. Unlike the operation for tetralogy of Fallot, the proper ligation or section of a patent ductus removes completely a pathological process and the final result is a normally functioning heart and great vessels. Thus far, nine years after the first successful correction of the defect, there has been no reason to feel other than that the operation is successful.

Everyone is familiar with the classical machinery murmur heard best in the second left interspace with a loud systolic and a softer diastolic component, which is characteristic of a patent ductus arteriosus. It is usually accompanied by a thrill. In the adult this characteristic murmur makes the diagnosis a comparatively simple matter when it is accompanied by the findings of a relatively wide difference between systolic and diastolic pressure particularly after exercise, by a systolic murmur heard over the apex, as well as by a characteristic roentgenographic pattern of the heart and an electrocardiogram which shows no right axis deviation. The criteria for diagnosis of patent ductus are thus established.

However, a careful study of the records of patients in whom patent ductus arteriosus was present although not discovered until operation or autopsy was done, indicates that there may be persons with this anomaly who do not present characteristic clinical evidence of it. Thus the to and fro murmur which is considered to be so intense, can actually vary from grade II to grade VI intensity. The diastolic component in turn may vary from an almost imperceptible grade I to grade V. There have been cases reported and confirmed by autopsy findings in which no murmur could be heard, presumably because of high pressure in the pulmonary artery.

In infancy and childhood, with which we are concerned, the common signs may be absent. The absence of the characteristic machinery murmur in infants and children renders the diagnosis of patent ductus arteriosus in this age period extremely difficult. In infancy the chest is so thin walled and the murmur which is limited to systole so widely transmitted, that the diagnosis cannot be made with certainty.

A sequence such as the following has been frequently encountered. A physician who has observed an infant from birth may note toward the end of the first year the development of a faint systolic murmur. At first the murmur may be indistinguishable from a functional murmur. Later it becomes so loud as to arouse suspicion of congenital malformation of the heart. Nevertheless, several years may elapse before the murmur develops the machinery quality which is so characteristic of patent ductus.

In recent years there have been added to the diagnostic aids two methods which utilize the x-ray. The first of these is the introduction of Diodrast, a radio-opaque dye, into the circulation, after which a series of roentgenograms is taken as the dye courses into and through the heart and great vessels. When the dye is introduced into the antecubital vein under pressure it may be found to remain longer in the chambers of the heart of a person having a patent ductus than it does in normal persons, presumably due to the passage of the dye from aorta into the pulmonary artery and back again through the lungs until it is finally diluted by the blood. However, it is a presumptive evidence and has not been found an infallible test.

A more successful modification has been the injection of the dye into the internal carotid artery, so that appearance of the dye almost simultaneously in the lungs and in the aorta may be looked upon as confirming evidence of a shunt between aorta and pulmonary artery.

Another method recently utilized is that of venous catheterization of the heart. A plastic catheter is threaded into a vein at the elbow, and successively into the right auricle, ventricle and pulmonary artery as well as into the pulmonary capillaries. This procedure gives valuable information when performed under fluoroscopic visualization; when the oxygen content of the blood in the heart, pulmonary artery and vena cava are measured and the blood pressures in the chambers of the heart and the great vessels are recorded. In the presence of a patent ductus arteriosus, the pressures in the right ventricle and pulmonary artery are equal. However, the oxygen saturation of the blood in the pulmonary artery is higher than that of the right ventricle, and the flow of the pulmonary capillaries exceeds that of the pulmonary artery.

It can be seen that if the pressure in the right ventricle exceeded that of the pulmonary artery, and the pulmonary blood flow were reduced, pulmonary stenosis must be suspected. The ligation or section of a ductus in such a case would destroy a valuable indirect source of blood to the lungs and might even result in death of the patient.

In conclusion it can be seen that the diagnosis of patent ductus arteriosus in the adults is in most cases not too difficult. There are, however, atypical

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cases which cannot always be differentiated by ordinary clinical means.

It must also be remembered that in infancy and early childhood the classical signs may be absent or incomplete and a definite diagnosis must in some instances be postponed until the child grows older, or the procedures outlined previously are utilized.

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QUESTION AND ANSWER

Question: In the absence of any physical findings in infants and children, what are the indications for diodrast studies or venous catheterization?

DR. ROBINSON: In the absence of any physical signs or symptoms, I do not think you could even suspect heart disease —there would be no indication for diodrast.

Metatarsus Varus

FRANCES BAKER, M.D., *San Francisco*

METATARSUS varus, a common finding in infants, may be of very slight degree or it may be so marked as to make one consider pes equinovarus in the differential diagnosis. The condition is usually neglected unless the deformity is very striking, as there is a tendency for the foot to straighten, thus giving a more normal external appearance. Apparently the foot can appear quite normal even to careful examination until the child starts weight-bearing. Then a definite varus of the forefoot presents itself, usually with over-activity of the abductor hallucis muscle, so that the first toe in particular swings into medial position, with the inturn of the entire forefoot notably increased in comparison with the resting position.

Perhaps the lack of attention to this condition lies in the fact that the literature contains reports stating that normal alignment is reached by the end of the first year.[5] In attempting to explain the cause of foot strain in adults and to understand why one individual might suffer from painful feet with or without such extrinsic evidences as corns, calluses, bunions, clawing, inversions or eversions, muscular spasm, and increasing loss of flexibility, while others can wear any type of shoe without discomfort, we became more interested in deviations from normal in children's feet. By careful roentgen examination of adult feet, we can rule out such congenital abnormalities as accessory scaphoids, coalitions, or specific disease which may be found in a small percentage of patients. However, in most instances, when dealing with the chronically painful foot, we can find variations in the forefoot consistent with failure of full evolutionary development.

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The human foot is probably derived from a primitive mammalian foot, retaining its primitiveness supposedly because of the terrestrial habits. Jones[1] has stated the opinion that such a foot belongs to the primitive members of the primate stem, the stem from which man and the other existing members of the primates branched apart and went their separate ways at a very early stage. With the orthograde posture the feet were forced to take on the weight of the body.[2] This demanded an increase in the tarsus both in weight and in size, while the metatarsals and phalanges shortened. The opposing first toe came to lie beside the second. The changes, therefore, are (1) a progressive reduction of the anterior section (metatarsophalanges) and an increase in the posterior section (tarsus); (2) a change in the relative length of the digits, especially a reduction of the dominant third and an increase in the size of the first; (3) a gradual decrease in the abduction of the first and incorporation into the main structure of the foot; (4) a downward and backward extension of the os calcis to form a true heel and hence the appearance of the true arch; (5) a notable increase in the rigidity of the foot to fit it for its new purpose.

Therefore, in the normal foot which has developed completely according to evolutionary plan, Morton[4] has shown that the weight of the body is borne by the heel and the metatarsal heads. The static stresses are borne by the rigid framework of the foot, which is made up of bones and ligaments, while the muscles supply the kinetic power, and aside from keeping the body in balance, act only during locomotion. The weight of the body on the two feet can be divided into 24 units, each foot supporting 12 units. These are equally divided between the os calcis posteriorly and the metatarsal heads anteriorly. The wide first metatarsal head

rests on two sesamoid bones supporting one unit, thus making six points of contact with the ground. The foot then represents a triangle with its apex at the os calcis and the opposite side formed by the metatarsal heads. A line drawn from the os calcis should pass between the second and third metatarsal bones in erect standing, thus dividing equally the weight-bearing areas. In running, the full weight of the body will be thrust upon the metatarsal head of one foot (24 units), half of this being thrust upon the first metatarsal head alone. Then a line from the os calcis falls between the first and second metatarsals.

The weight of the body is transmitted through the astragalus (talus) to the os calcis, which forms a table upon which it rests. The bones of the midtarsal region represent a dome-shaped transverse arching, increasing the structural strength for forces applied vertically and converging the stresses toward the separate metatarsals, which are arched proximally but flattened distally so that their heads lie in a single plane.

The first metatarsal then is of particular importance to the internal mechanism of the foot: (1) It supports the medial side of the foot and prevents depression of the sustentaculum tali, thus preventing pronation. (2) It supports a major share of static stresses in locomotion. (3) It gives support to the astragalus, which is the center from which static stresses are distributed.

Any failure of normal evolutionary development, then, which interferes with the stability of the first metatarsal or changes the balance of weight-bearing so that the foot cannot conform to shoes or to long standing on hard surfaces is a potential cause for strain.

Barring severe trauma, paralyses, infections, etc., true foot strain can be attributed to certain deviations from the so-called normal foot which are inherited and represent a failure of full evolutionary development. Morton has defined certain anatomic variations which lead to definite strain: (1) a short first metatarsal, or (2) posteriorly placed sesamoids under the first metatarsal, and (3) hypermobility of the first metatarsal segments (including the first cuneiform bone which moves with the metatarsal). The short heel cord is considered as an extrinsic factor. He does not mention the metatarsus primus varus which is seen so frequently, but it does belong under the heading of "hypermobility of the first metatarsal segment." It has been discussed by many authors. Lapidus[3] described this condition as a primary cause of hallux valgus, since a large degree of angulation (10 to 19 degrees) exists between the first and second metatarsals with the first metatarsal in abduction.

In addition, I wish to add still another factor closely related to these as a cause of strain, namely, metatarsus varus, or a varus of the entire forefoot. This condition does persist into adulthood and can be easily demonstrated roentgenologically. Except by careful x-ray examination, it is difficult to recognize even when it is suspected, because the angle between the first and second metatarsals is normal since the entire forefoot is in varus and sufficient adjustment takes place in the tarsus to give a fairly straight medial line to the foot. We find, then, that in a large percentage of cases of foot strain in adults, the intrinsic causes are: (1) short first metatarsal; or posteriorly placed sesamoids under the first metatarsal; or hypermobility of the first metatarsal segment; (2) metatarsus varus, with or without metatarsus primus varus; and (3) the very important extrinsic factor—short heel cord. If individuals having feet of this type were not forced to wear shoes never designed for them, or to walk on hard surfaces which give no flexible support to the first metatarsal, then this deviation from the so-called normal would have little or no importance as these are fundamentally strong feet, failing only of full evolutionary development. The abnormalities are of course familial.

Recognizing that metatarsus varus does not disappear in childhood but persists in the adult foot, the question arises as to what correction should be attempted in infants. The amount of metatarsus varus in babies varies tremendously. Two infants in a series observed by the author gave the appearance of having clubbed feet, showing not only a pronounced varus deformity but the inversion of the tarsus and the short heel cords as well. The ease with which the last two elements were corrected with casts seemed enough to rule out true club-foot, but the varus deformity in one child has remained to a considerable degree; the feet of the other child show good correction at two years of age but the child is still wearing corrective shoes. The correction of the feet of the first child should have been much better had not an attempt been made to use leather molds after casting for only one month.

Pediatricians are realizing that routine development does not overcome the varus deformity but rather that it deserves special consideration. In spite of this, frequently babies with the deformity are not referred for orthopedic consultation until they begin to walk. Certain pediatricians who have been particularly alert to this condition, and who ordinarily refer patients for early care, have stated that the feet of those whom they referred late, appeared normal until weight-bearing began. Usually, the condition can be recognized immediately after delivery, and treatment should be started within the first two to three weeks. This simplifies the care as the child is ready for shoes by the time it is ready to walk, and it does not have to be constrained by casts with all the attending increase in care after walking is begun.

The author has placed casts on 32 of 60 babies observed for metatarsus varus and improvement has resulted. If it is decided that a correction should be forced, then casts are necessary, as no other simple support, such as a leather mold, will produce a shift in the forefoot. Casting is started at as early an age as possible and carried on for at least four or

five months. The casts are applied one week and wedged open on the medial side at the tarso-metatarsal junction the next week. They are changed completely every two weeks. Inasmuch as this condition is an inherited characteristic, the growth factor has to be considered, and, though the varus deformity can be corrected, if a wide angle is present between the first and second metatarsals this tends to persist.

When the condition is severe, there is often a tight medial band of soft tissue which is hard to stretch. When the varus is marked, and particularly when this medial band is present, casts should be used until appropriate shoes can be fitted. Although the first metatarsal may not entirely lose its broad angle with the second, the whole forefoot will be brought into better line with the tarsus and the ratio of weight-bearing improved. This in itself will permit the wearing of a more usual shoe. After the casts are removed, as the child is beginning to walk, shoes can be fitted to the opposite foot. Later the pronator type of shoe can be used or shoes of good quality can have a 1/8 to 3/8-inch lift on the lateral part of the sole and medial portion of the heel to thrust the forefoot into line with the tarsus. It is particularly important that the shoes be closely and accurately fitted. They should be worn at night as well as during the day.

When the varus deformity is of a moderate degree and passive correction is easily obtained, stretching by grasping the tarsus and moving the metatarsals lateralward at the tarsometatarsal junction should be done many times each day. When firm shoes can be fitted, they can be applied with the corrections described previously.

SUMMARY AND CONCLUSIONS

Metatarsus varus should receive more attention by pediatricians since it may not disappear but is frequently seen in adult feet and is a cause of strain and deformity. It can be present with metatarsus primus varus, with Morton's syndrome of short first metatarsal and hypermobility of the first metatarsal segment, or it can be present without evidence of these, in which case it is impossible to recognize without roentgenograms.

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What's New in the Treatment of Erythroblastosis

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THE Race-Fisher system of nomenclature of CDE-cde for the Rh-Hr system in the antigenic make-up simplifies the ever-increasing complexity of the problem of treating erythroblastosis and should be adopted universally. This system makes it possible to tell at first glance which persons will be sensitized, particularly in the rarer forms. The common single chromosome combinations are CDe, cde and cDE. If a woman with the genetic formula cde-cde (Rh-negative) is mated with a man whose genetic formula is CDe-CDe, (homozygous Rh-positive), the offspring will have the genetic formula of CDe-cde or always Rh-positive. If, however, this woman is mated with a man whose genetic formula is CDe-cde (a heterozygous Rh-positive), the offspring will have a 50-50 chance of being a cde-cde (Rh-negative). Formerly it was thought the Rh-negative lacked antigens, but we now know that they have three antigens known as c, d and e which are poor antigens and result in the rarer Hr factor. The anti-D serum has an 85 per cent specificity, the anti-c serum is important for the determination of heterozygosity, and anti-e serum for determining the 14 per cent who have a genetic formula, CDe-cDE.[6]

Until recently there was but one known method of treating erythroblastosis—multiple transfusions with Rh-negative blood, which was not adequate in all cases. Today a procedure known as exsanguination and replacement transfusion is available.

Exsanguination and replacement transfusion is indicated if there are severe signs and symptoms of erythroblastosis present at birth or if there is a family history indicative of chromosome incompatibility plus a strongly positive result of a Coombs' test,[5] conglutination test,[8] or gelatin test,[4] even though there is very little or no evidence of the disease at the time of birth. It remains to be seen whether exsanguination and replacement transfusion is advisable in cases in which there is strongly positive agglutination by one of the above methods but no history indicative of erythroblastosis and little or no evidence of the disease in the infant. There are several physicians in this country who feel that the procedure should be carried out in such circumstances, and yet in one of our recent cases only two transfusions were required. It must be emphasized that there are very mild cases of erythroblastosis fetalis in which the infant recovers without treatment, and some moderately severe cases in which multiple transfusions are effective.

The umbilical vein is used for transfusions done within 12 hours after delivery; for those carried out later, entry is made into the inferior vena cava by way of the great saphenous vein exposed in the upper thigh.[1] The use of the Diamond plastic catheter No. 18-19,[3] sterilized in Zephrin, for cannulizing these veins is the accepted procedure. Blood is withdrawn 20 cc. at a time and replaced with an equal amount of Rh-negative blood, the total of such exchanges varying from 250 to 500 cc. of blood, the amount depending usually on the severity of the disease. If anemia is present, 30 to 50 cc. more is given than is removed. Heparin, 10 mg. in normal saline, may be used as a rinse to keep the apparatus free of clots. As a final step 5 cc. of 10 per cent calcium gluconate is introduced through the cannula to counteract the excess citrate. It must be given well diluted, and better yet, in divided doses, to avoid heart block. Other procedures, such as withdrawal from the fontanel,[7] radial artery,[7] or femoral artery and introduction through the saphenous vein are used occasionally. Malony prefers to withdraw the blood from the umbilical vein and introduce the blood through the saphenous vein because in one case in which the blood was introduced through the umbilical vein, autopsy showed the mesenteric veins were thrombosed, resulting in a gangrenous bowel; and in another case free blood was found in the peritoneal cavity. Maintenance of oxygen supply and body temperature during the procedure is of utmost importance. Chemotherapy for four or five days thereafter is definitely indicated.

Induction of labor or Cesarean section for removal of the fetus prematurely in order to treat erythroblastosis should be used with reserve because the mortality rate from prematurity is greater than from the disease and actual benefit of the earlier treatment is very doubtful.

Beyond the measures now used, one other way of lowering the mortality rate from this disease is to have some program in each community whereby every pregnant woman may have the benefit of the Rh studies for a fixed price and those requiring further follow-up studies may have them without additional cost. In Pasadena such a program has proven very effective not only in lessening the financial burden of the Rh-negative mothers but in making it possible to alert the pediatrician for possible trouble.

The next step should be to prevent the development of this disease. We know that only one in every 25 of the Rh-negative wife and Rh-positive husband combinations have children with erythroblastosis and that in the presence of two antigens, antibodies will be produced for the stronger one. Therefore, it may be wise to give typhoid vaccine to Rh-negative sisters

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of Rh-negative mothers who have had infants with erythroblastosis, provided, of course, the blood of the sister's husband is such that erythroblastosis might be expected in the couple's offspring.

Bloxsom and Matthaei[2] have discovered a new factor, the anti-Rh antigen-antibody factor, which has been found to be present in high concentrations in Rh-negative mothers who, although having Rh-positive husbands, have normal offspring. As this factor has been found in Rh-negative male blood donors also, serum from these donors is being given to pregnant women in the hope of preventing or minimizing the disease in their children. Several other workers are using haptens, allergicil and normal saline for purposes of desensitization. Even if the anti-body titre can be reduced or the level maintained, it may not prove to be the answer, for frequently there is a marked discrepancy between the anti-body titre and the severity of the disease. It will be some time before work along this line can be fully evaluated and it will be interesting to follow the studies.

Another possibility for those having lost one or more infants and with husbands who are homozygous is artificial insemination with semen from an Rh-negative donor.

The publicity that has been given to the importance of erythroblastosis has caused undue alarm, particularly for young couples who have a hazardous Rh combination. It is the duty of physicians to explain to such persons that the disease occurs in only one infant in 25 whose parents have the combination, and that with present methods of treatment the mortality rate among infants who have the disease is about 10 per cent.

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QUESTIONS AND ANSWERS

Question: There is a question as to the indications for exsanguination transfusion. Let us take a child from the time of birth—whether or not he should have a transfusion.

DR. KIRCHDOERFER: If the child has all the signs and symptoms, particularly severe jaundice at birth, I think you go right ahead and assume he has erythroblastosis. If there is a family history of erythroblastosis and a positive reaction to agglutination tests or Coombs' test or other test, immediate exsanguination transfusion is probably indicated even though clinically the child does not seem to have the disease.

Question: Why give typhoid vaccine to mothers?

DR. KIRCHDOERFER: Weiner stated when you have two antigens present, the antibodies will be formed for the stronger antigens, and with that in mind it is believed that it disperses the others. That is just an idea that Weiner stated. I don't believe anybody ever tried it, or that there is anything on it—just a thought.

The Place of the Non-Operative Treatment in the Therapy of Perforated Peptic Ulcer

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THE treatment of patients with perforated peptic ulcer is a special problem in the emergency service of large city hospitals. Although surgical closure of the perforation is usually successful, the treatment of the patient with long-standing perforation or of one with generalized peritonitis is far from satisfactory. Recently[6] a report has been issued advocating the non-operative treatment of perforated ulcer. A series of cases has been studied to determine whether non-operative methods might have avoided any of the fatalities, and to ascertain the type of case suitable for non-operative care.

The present study is based upon 265 cases of perforated ulcer observed between July 1942 and July 1947. One hundred forty-eight were gastric ulcers and 117 duodenal ulcers. During this same period the medical services treated 244 patients with gastric and 529 with duodenal ulcers.

Butler[2] reported the experiences of this hospital in 251 cases in 1934. At that time the mortality rate was 24.5 per cent, which compared favorably with a review of 2,823 cases with a mortality rate of 29 per cent reported in the literature between 1896 and 1931. At that time, non-operative treatment was reserved in the San Francisco Hospital for those patients with perforated ulcers who were moribund from generalized peritonitis.

Many surgeons have pointed out the following factors which lead to an increase in the mortality rate in this disease: the duration of perforation before closure, the anatomical site of the ulcer, the volume and type of contents of the stomach at the time of perforation, the intake after perforation, the reaction of the peritoneum to infection, and the general condition of the patient at the time of perforation. The importance of the time factor is the simplest to demonstrate statistically. DeBakey[3] in 7,683 cases collected from the literature found the mortality rate in the first six-hour period to be 10.5 per cent, in the second six-hour period 21.4 per cent, in the third six-hour period 38.5 per cent, in the fourth six-hour period 62.4 per cent, and thereafter 61.5 per cent. These figures are in general agreement with other reports.[1,7] Taylor[6] has reported a series of 28 cases treated without operation. He argues against automatic surgical intervention in which no distinction is made between simple perforation and perforation in which the effects of peritonitis are the most disabling. Unfortunately, in only two of his patients was free air shown under the diaphragm so that from the abstracts presented in his paper one cannot be certain that these patients were not suffering from penetrating ulcers rather than from true perforations into the free peritoneal cavity.

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During the period covered by the study, ten patients with proven perforated ulcers recovered without operation on the following regimen: constant gastric suction through a Levine tube, nothing by mouth, parenteral glucose solution and vitamins and sedation. Antibiotics were used in only three cases. Three patients refused operation, but in seven cases operation was not performed because of a serious complication, or because the patient appeared to be improving clinically. It is interesting that an ulcer in one patient (Case 4) perforated three times and the patient accepted operation for the second perforation only. In all cases except Case 6 free air was demonstrable by roentgenogram. In this patient an abscess was found walled off by the liver at the site of perforation. In the experience of this hospital, free air is present in 85 to 90 per cent of all cases of perforated ulcers. Its absence suggests that the perforation has been rapidly sealed off. If no free air is present in a patient who is clinically improving, we believe it safe to start out with the non-operative treatment.

RECOVERY WITHOUT OPERATION

1. A man of 63 complained of abdominal pain of 18 hours' duration. He had a four-year history of ulcer proven by roentgenograms. Examination showed abdominal tenderness and spasm. Leukocytes numbered 16,800. There was free air under the right diaphragm in "considerable" quantity. As the patient refused operation, he was treated with gastric suction and intravenous fluids. He was well when discharged 15 days after entry. The patient died in this hospital three years later from hemorrhage from the gastro-intestinal tract.

2. A man of 44 had acute abdominal pain of one hour's duration. He was said to have had a perforation of stomach ulcer eight years before, and was hospitalized but refused operation and recovered. Examination showed rigid tender abdomen with grunting respirations. A small amount of air was seen under the diaphragm by roentgenogram. The patient again refused operation and was treated by gastric suction, penicillin and intravenous fluids. Recovery was rapid and he was released from the hospital seven days later.

3. A man of 66 entered with complaint of acute onset of severe abdominal pain 12 hours previously. The patient had a long history of peptic ulcer proven by roentgenogram. He was operated on for perforation six years before. Examination showed a very sick man breathing with difficulty. Abdomen was spastic and tender and silent. Free air as well as pulmonary congestion at both bases was demonstrated by roentgenogram. Leukocytes numbered 20,300. He was treated with gastric suction, penicillin and intravenous fluids and slowly recovered. Signs of subdiaphragmatic abscess developed including neighboring fluid in the right chest. Both slowly absorbed and the patient was discharged well 34 days after entry.

4. A man of 41 entered 14 hours after the onset of acute abdominal pain. Examination showed tenderness in the abdomen and free air was shown under the right diaphragm by roentgenogram. Leukocytes numbered 22,000. The patient refused operation and was treated by gastric suction and intravenous fluids. He was discharged well 14 days later. The

patient reentered 19 months later. He had been operated upon for perforated ulcer in another hospital eight months previously. Again on entry to the San Francisco Hospital signs of peritonitis with free air under the diaphragm were found. The patient again refused operation and recovered sufficiently to be released one week later.

At a third and fourth entry four years later, he had no further perforations but was still suffering from ulcer pain.

5. A man of 53 entered 12 hours after the onset of acute abdominal pain. Abdominal examination showed tenderness in the upper quadrants only. Temperature was 101° F. Leukocytes numbered 17,000. Free air under the diaphragm was shown by roentgenogram. The chest was clear. The patient refused operation and was treated by gastric suction and intravenous fluids. He recovered rapidly and was released five days later.

6. A man of 57 entered five days after the onset of acute abdominal pain. He had a long history of ulcer. The patient was studied carefully and a diagnosis of duodenal ulcer made. No free air was noted. Thirteen days after entry, laparotomy was performed. A small abscess was found where a duodenal ulcer had perforated and had been walled off by the liver. Gastric resection was performed. Convalescence was uneventful.

7. A man of 38 entered with complaint of pain in the abdomen, nausea and vomiting associated with fever and weakness of two weeks' duration. He was said to have had tarry stools just before entry. Examination showed a sick man with a tender distended abdomen. Hemoglobin was 42 per cent and leukocytes numbered 16,000. Flat roentgenogram showed free air under the right diaphragm. With supportive therapy including gastric suction, intravenous fluids, transfusions and sulfadiazine, the patient slowly improved.

Twenty days after entry, a right subphrenic abscess was drained. The patient slowly recovered. Gastro-intestinal studies 41 days after entry demonstrated a large penetrating ulcer on the superior margin of the duodenum.

8. A man of 52 entered 42 hours after the onset of acute abdominal pain. The patient had had a perforated ulcer closed by operation at another hospital two months before the present episode. Examination showed the patient to be resting comfortably. The abdomen was tender throughout but no spasm was found. Peristalsis was hypoactive. Leukocytes numbered 15,000. The urine was normal. A flat roentgenogram showed elevated leaf of right diaphragm and wide separation of the loops of small bowel, suggestive of fluid, but no free intraperitoneal air.

The patient was treated with gastric suction, intravenous fluids and general supportive therapy with improvement. Gastro-intestinal studies, 14 days later, showed a duodenal ulcer from which a thin track of barium was seen to leak cephalad.

9. A man of 55 entered with acute abdominal pain and vomiting for the preceding 48 hours. Examination showed a distended silent tender abdomen. Leukocytes numbered 20,000. A flat roentgenogram showed "considerable" subdiaphragmatic air on both sides as well as gas in the small bowel. The patient was treated with gastric suction, penicillin, intravenous fluids and other supportive measures. He rapidly recovered and was discharged 13 days after entry. The patient was seen again seven months later for a minor fracture. He had no further gastro-intestinal symptoms. Gastro-intestinal studies showed "Spastic duodenal bulb, probably with duodenal ulcer."

10. A man of 56 with moderately extensive pulmonary tuberculosis entered 26 hours after the onset of acute abdominal pain. Examination showed tenderness and spasm in the upper belly. Abdomen was silent. Leukocytes numbered 30,000. Free air was noted under the right leaf of the diaphragm. Non-operative treatment was undertaken as symptoms and signs seemed to be subsiding. The patient recovered satisfactorily and gastro-intestinal studies three weeks later showed a penetrating duodenal ulcer. The patient had a thoracoplasty four years later, at which time he had no further gastro-intestinal complaints.

The patients in the following three cases (11, 12 and 13), although operated upon, would have recovered without operation, as the perforation was sealed. In none of these cases was free air noted by roentgenogram.

11. A man of 56 entered with a five-day story of abdominal pain. The onset was followed by persistent vomiting and intermittent hiccough. The patient had previous entries for luetic heart disease and cirrhosis of the liver. Examination showed the patient to be acutely ill. Abdomen was distended and tender especially in the right lower quadrant. Leukocytes numbered 18,200. A roentgenogram showed no free air but considerable gas in the small bowel. Operation was planned through a McBurney incision. The appendix was normal but purulent fluid present and a mass was seen in the right upper quadrant. The McBurney incision was closed and a right rectus incision made. A large mass of omentum as well as indurated colon were plastered to the duodenum. It was considered that this was a sealed duodenal ulcer so nothing further was done. The patient was treated with gastric suction, penicillin and intravenous fluids. He recovered satisfactorily. Two subsequent hospital entries have been made for heart disease.

12. A man of 61 entered ten hours after the onset of abdominal pain. The patient was doing heavy work when he was suddenly struck by pain in the left upper quadrant and when seen at another hospital was said to be in mild shock. At that hospital, a history of alcoholism and chronic stomach trouble was obtained. This the patient denied on entry to the San Francisco Hospital. Examination on entry showed no evidence of shock. Pain and tenderness were limited to the epigastrium. The patient had a fever. Leukocytes numbered 16,200. No free air was noted by roentgenogram; the diagnosis was in doubt. Some examiners considered perforated ulcer, others ruptured spleen, pancreatitis. Treated with gastric suction, penicillin and intravenous fluids, the patient improved. Gastro-intestinal studies 13 days later showed a large gastric ulcer on the lesser curvature, posterior wall. One month after the perforation, the patient had a gastric resection for a large gastric ulcer which had perforated into the undersurface of the liver.

13. A woman of 37 entered two hours after the onset of acute abdominal pain. The patient had a long history of duodenal ulcer which had been demonstrated by roentgenogram at another hospital. Examination showed a tender abdomen, not board-like in character. Peristalsis was active. Leukocytes numbered 16,000. No free air was seen by roentgenogram. With nasal suction and intravenous fluids, the patient improved over the course of the next few hours.

The abdomen was opened about eight hours later. A large firm anterior indurated prepyloric ulcer was found with a tiny perforation in its center. This had been sealed over with fibrin. Air and fluid could not be forced out of the hole. Attempts to close over the area so narrowed the pylorus that a gastric resection was done. The patient recovered satisfactorily and was discharged 15 days later.

Occasionally a large amount of free air may be found with evidence of peritonitis and yet careful search will fail to reveal the site of the perforation.

14. A man of 69 entered 38 hours after the onset of acute abdominal pain. The patient was known to have had peptic ulcers for 16 years prior to entry. He had been treated with Sippy powders and diet. On entry examination, he appeared acutely ill. Abdomen showed signs of generalized peritonitis.

Temperature was 105° F. Leukocytes numbered 11,400. Flat roentgenogram showed large amounts of air under both diaphragms. The abdomen was opened through a right rectus incision with ether anesthesia. A large amount of free fluid containing fibrin was found. Peritonitis was generalized. No source of the air could be found after careful and prolonged inspection of the abdominal viscera and the abdomen was closed. Culture of the peritoneal fluid showed a non-hemolytic streptococcus and an occasional Gram-rod.

After a stormy course, the patient recovered. A histamine test meal showed a high acid content. Gastro-intestinal studies and barium enema demonstrated no lesion.

The patient had another entry one year later at which time he had had no further gastro-intestinal symptoms.

DEATHS WITHOUT OPERATION

Fifteen patients died from perforated ulcers in whom no operation was performed because the patients were moribund on entry.

15. A woman of 47 entered with a complaint of four days of acute abdominal pain. Examination showed an obese woman moribund and in shock. The patient died shortly after entry. Autopsy showed a perforated ulcer with generalized peritonitis.

16. A man of 62 entered with acute abdominal pain of five days' duration. Examination showed a very ill man breathing with considerable difficulty. There were signs of pneumonia in the chest. The abdomen was silent and distended. Free air was seen by roentgenogram under both diaphragms. Leukocytes numbered 9,950. In spite of penicillin, oxygen, gastric suction and supportive therapy, the patient died two days after entry. Autopsy showed a perforated ulcer with generalized peritonitis.

17. A man of 46 entered with a three-day story of acute abdominal pain. He had been drinking heavily for some time before the onset of the pain and continued to do so afterward. Examination showed a sick man with obvious generalized peritonitis. Free air was seen under the diaphragms by roentgenogram. Leukocytes numbered 13,000. The patient was started on gastric suction and supportive therapy but died a few hours after entry. Autopsy showed a perforated gastric ulcer with generalized peritonitis.

18. A man of 70 entered two or three days after the onset of acute abdominal pain. He had a seven-year history of indigestion. Examination showed an old man in shock with signs of generalized peritonitis. Free air was seen under the diaphragms by roentgenogram. Leukocytes numbered 5,700. The patient died 12 hours after entry. Autopsy showed a perforated duodenal ulcer with generalized peritonitis.

19. A man of 45 entered with a 12-hour story of acute abdominal pain. The story was vague as the patient had been drinking heavily. Examination showed a very sick man in moderate shock with a board-like silent tender abdomen. Leukocytes numbered 7,000. Free air was seen under both diaphragms by roentgenogram. The patient died three hours after entry. Autopsy showed a perforated gastric ulcer with generalized peritonitis.

20. A man of 78 entered in such poor general condition that no history was obtainable. Examination showed him to be in shock and to have a rigid tender spastic abdomen. He was anemic. Erythrocytes numbered 2 million and leukocytes 32,800. Free air was seen under the right diaphragm by roentgenogram. In spite of supportive therapy, the patient died three days after entry. There was no autopsy.

21. A man of 57 entered 18 hours after the onset of acute abdominal pain. Examination showed a very sick, cyanotic, obese male in shock with the abdominal signs of generalized peritonitis. Leukocytes numbered 3,150. Diagnosis of mesenteric thrombosis was made. The patient died in 24 hours in spite of intensive supportive therapy. Autopsy showed a perforated duodenal ulcer with generalized peritonitis.

22. A man of 72 entered with a history of 16 days of vomiting, chest pain and shortness of breath. Examination showed a sick old man with silent distended tender abdomen. Flat roentgenogram showed free air and fluid under the right diaphragm. Leukocytes numbered 4,300. The patient refused operation and he died 24 hours later. Autopsy showed a ruptured gastric ulcer with generalized peritonitis, mitral stenosis and insufficiency, and cardiac failure.

23. A woman of 70 entered with a four-day story of acute abdominal pain and vomiting. The patient had a 20-year history of epigastric distress after eating. Examination showed an obese old woman who appeared moderately ill. Abdomen was tympanitic, tender and distended. Free air was demonstrated under the left diaphragm by roentgenogram. Leukocytes numbered 10,300. In spite of transfusion, intravenous fluids and gastric suction, the patient died four days after entry. Autopsy showed a perforated ulcer at the pylorus with generalized peritonitis.

24. A man of 63 entered 24 hours after the onset of acute abdominal pain. The patient was extremely ill and in mild shock. Examination showed signs of generalized peritonitis. Leukocytes numbered 15,000. Free subdiaphragmatic air was seen by roentgenogram. The patient died seven hours after entry. Autopsy showed a perforated ulcer with generalized peritonitis.

25. A man of 63 entered with a three-month history of abdominal pain after eating. Examination was not remarkable. At 3:30 the morning after entry, the patient complained of severe abdominal pain. Examination at this time by the medical house officer showed peristalsis present and no localizing abdominal signs. An enema was given. Examination was made by the surgical house officer a few hours later. He likewise believed the patient had a penetrating ulcer. The patient died a few hours later, two days after entry. Autopsy showed a generalized peritonitis from perforation of a gastric ulcer.

26. A man of 75 was brought in moribund and died a few minutes later. Autopsy showed a perforated duodenal ulcer with generalized peritonitis.

27. A woman of 47 entered four days after the onset of acute abdominal pain. Examination showed an obese female in shock. The patient died a few minutes after entry. Autopsy showed a perforated peptic ulcer with peritonitis.

28. A man of 58 entered with a 48-hour story of acute abdominal pain, vomiting and collapse. He had a 15-year history of peptic ulcer proven by roentgenogram. Examination showed a very sick man with signs of generalized peritonitis. Leukocytes numbered 2,500. Free air was seen under the diaphragms by roentgenogram. During the next 24-hour period he slipped further into shock in spite of supportive treatment and died. Autopsy showed a perforated gastric ulcer with generalized peritonitis.

29. A man of 49 entered with a complaint of sudden epigastric pain of three days' duration. He had a two-year history of epigastric distress relieved by soda. Examination showed an obese man in mild shock. The abdomen was silent, tender and spastic. Leukocytes numbered 20,000. Free air was seen beneath both diaphragms by roentgenogram. An ether anesthetic was started but the patient suddenly went into collapse, pulse became extremely rapid, cyanosis marked. Anesthesia was stopped and oxygen and transfusion were started. Shortly thereafter, the patient died. Autopsy revealed a perforated ulcer at the pylorus with no attempt at sealing. There was a generalized peritonitis.

The deaths from perforation following surgical closure were studied to see if any of these patients might have been saved had they been treated with-

out operation. There were 17 cases in this group. It is possible that Cases 33, 39, 45 and 46 might have survived without operation. These were older patients with perforations in the third group in DeBakey's classification. They were all chronically sick before the perforation occurred so that the risk of operation was correspondingly larger.

DEATHS FOLLOWING OPERATION

30. A man of 54 entered two hours after the onset of acute abdominal pain. He had a long history of indigestion. Examination showed an acutely ill man with a board-like tender silent abdomen. Leukocytes numbered 20,000. Flat roentgenogram showed free air under the right diaphragm and increased density in the right lower lobe.

The abdomen was opened through an upper right paramedian incision, using ether anesthesia. An 8 mm. perforation was found and closed. Six hundred cubic centimeters of peritoneal fluid were aspirated, cultures of which showed no growth after 72 hours. The patient did very poorly. The signs of peritonitis and obstruction supervened and he died 11 days after entry.

31. A man of 44 entered with an 18-hour story of acute abdominal pain. He had a five-year history of indigestion and epigastric distress. Examination showed a very sick patient with a distended silent tender abdomen. Leukocytes numbered 16,500. Free air under the diaphragms was seen by roentgenogram.

The patient was prepared for operation with plasma and intravenous fluids. Then under ether anesthesia a right upper rectus incision was made. Five thousand cubic centimeters of bile-stained fluid was aspirated. A 6 mm. perforation in the anterior wall of the duodenum was closed. The patient recovered satisfactorily from the operation but wound infection, parotitis and atelectasis then developed and the patient died on the 16th day. Autopsy confirmed the diagnoses and revealed a left pleural effusion.

32. A man of 68 entered 19 hours after the onset of acute abdominal pain. The patient had a long history of indigestion, tarry stools and alcoholism. Examination showed a very sick old man in shock. Abdomen was rigid and silent. Blood pressure was 65 mm. of mercury systolic, 0 diastolic. A large amount of free air was seen under both diaphragms by roentgenogram. Leukocytes numbered 8,500.

Prior to operation, the patient was given 500 cc. of whole blood, 500 cc. of plasma and 1,0000 cc. of glucose in saline without much improvement. Under ether anesthesia, the abdomen was opened and a large amount of purulent fluid aspirated. An 8 mm. perforation was found on the anterior wall of the stomach. This was sutured. After transfusion of 500 cc. of blood, the patient improved somewhat. With gastric suction, penicillin and intravenous fluids, the signs of peritonitis slowly subsided. But the patient began to fibrillate and passed decreasing amounts of urine. The nonprotein nitrogen slowly rose to 252 mg. per 100 cc. as the urinary output fell off. Fourteen days postoperatively, the patient began to secrete urine again but expired suddenly on the 17th postoperative day. No autopsy was obtained.

33. A man of 72 with a ten-year history of "stomach trouble" was admitted to the urological service because for 14 hours he had been unable to urinate. As most of the difficulties seemed to be associated with prostatic obstruction, he was treated for this lesion. Eighteen days after entry, a transurethral resection was done. Three days later abdominal distention, tenderness and spasticity developed. Flat roentgenogram showed no free air but cystograms were interpreted as showing a ruptured bladder. When a suprapubic cystostomy was performed, no rupture was found in the bladder but cloudy peritoneal exudate was seen coming from the upper abdomen. An upper abdominal incision was made and a large perforated gastric ulcer found after considerable difficulty. The surgeon was not sure that the patient did not have an old gastro-enterostomy with a perforated marginal ulcer. The patient was in very poor condition at the end of this procedure. In spite of transfusions, penicillin and other supportive therapy failed and the patient died nine days after operation. Autopsy showed multiple intraperitoneal abscesses. The sutured ulcer was 8 cm. from the cardia on the greater curvature. There was also a moderately severe cystitis and pyelonephritis as well as bronchopneumonia.

34. A man of 57 entered with acute abdominal pain which had begun four or five days before. The pain had been constant since, associated with vomiting, and radiation to the shoulders. The patient had been drinking and he was known to have had "stomach trouble" for many years. Examination showed moderate distention and tenderness throughout the abdomen. A large amount of free subdiaphragmatic air was seen on the flat roentgenogram. Leukocytes numbered 9,600. A laparotomy under cyclopropane revealed a perforation of the stomach on the lesser curvature, anterior surface, close to the esophagus. Postoperatively the patient developed signs of pneumonia and died on the eighth day. Autopsy showed the cause of death to be generalized peritonitis.

35. A woman of 47 entered with acute abdominal pain of nine hours' duration. Examination showed a rigid tender silent abdomen. Leukocytes numbered 9,000. Free air was seen under both diaphragms by roentgenogram. An operation under cyclopropane revealed a large amount of free fluid which cultured a non-hemolytic streptococcus. A 1 cm. perforation was found on the anterior surface of the stomach 2 cm. from the pylorus. This was sutured. In spite of penicillin, gastric suction and supportive therapy, the patient died on the second postoperative day. No autopsy was obtained.

36. A man of 47 entered 48 hours after the onset of acute abdominal pain. He had a 20-year history consistent with peptic ulcer. Examination showed the patient to be acutely ill but not in shock. There were the usual abdominal signs of generalized peritonitis. Leukocytes numbered 13,400. Free air was seen under the right diaphragm by roentgenogram. Operation under local anesthesia revealed turbid peritoneal fluid and a perforated gastric ulcer on the lesser curvature near the pylorus. This was closed. The patient became much sicker postoperatively, developing delirium tremens and bilateral pneumonia. He died six days after entry. No autopsy was obtained.

37. A man of 62 entered 30 minutes after the onset of acute abdominal pain. He had been treated in this hospital for the preceding two years for gastric ulcer. Examination showed an old man with a board-like tender silent abdomen. Leukocytes numbered 10,300. Free air was seen under both diaphragms by roentgenogram. Operation about five hours after perforation, using spinal anesthesia, revealed 600-800 cc. of peritoneal fluid containing food particles. The perforation which was on the lesser curvature of the stomach near the pylorus was sutured. The patient recovered satisfactorily and was discharged 18 days postoperatively. He reentered the hospital two weeks later complaining of abdominal pain, swollen joints, fever and diarrhea. The exact nature of the illness was not determined. One morning without warning he complained of severe abdominal pain, went into shock and died. Autopsy demonstrated that a residual liver abscess of long standing had suddenly ruptured into the free peritoneal cavity.

38. A man of 58 was brought into the urological ward in an alcoholic state by the police because of urinary incontinence. He was covered with filth and on the verge of delirium tremens. Six days after entry he complained of severe abdominal pain. Examination revealed a tender spastic abdomen. Considerable air was seen under both diaphragms by roentgenogram. The patient was operated upon under cyclopropane about eight hours later. Turbid fluid was encountered and then a large abscess cavity was entered completely surrounded by omentum. After this had been evacuated, a perforation was found in the duodenum. This was closed. The patient did not recover from the shock of the procedure and died 12 hours later. No autopsy was obtained.

39. A man of 69 entered 16 hours after the onset of acute abdominal pain. The patient stated he had been in poor health with abdominal pains for one year and had lost 25 to 30 pounds. Examination showed a sick old man with abdominal signs limited to the upper abdomen. Leukocytes numbered 28,000. Free air was seen under the right diaphragm by roentgenogram. Operation under cyclopropane revealed a perforated prepyloric ulcer. Postoperatively the patient developed bronchopneumonia, parotitis and died on the 14th day. Autopsy confirmed the clinical findings. The peritonitis had been adequately handled.

40. A man of 73 entered 18 hours after the onset of acute abdominal pain. He had a ten-year history of intermittent abdominal pain relieved by soda. Examination showed a sick old man with a rigid tender silent abdomen. Leukocytes numbered 6,650. Free air was seen under the diaphragms by roentgenogram. Operation under cyclopropane revealed a large amount of turbid fluid and 5 mm. perforation at the pylorus. The peritoneal fluid showed hemolytic streptococci and E. coli on culture. Postoperatively the patient had considerable urinary difficulty which necessitated constant drainage. Although his abdominal signs subsided, unilateral pneumonia developed, and in spite of supportive therapy he died on the 14th postoperative day. No autopsy was obtained.

41. A man of 67 entered 15 hours after the onset of acute abdominal pain. Examination showed tenderness and spasm in the right upper quadrant. No free air was seen by roentgenogram. Leukocytes numbered 13,700. Operation under local anesthesia with a diagnosis of acute cholecystitis revealed a large amount of free peritoneal fluid. A 4 mm. perforation was found in the anterior surface of the stomach 3 cm. from the pylorus. This was sutured. The patient died two days later. Autopsy showed generalized peritonitis, with smears showing numerous cocci. There was an acute ulcerative esophagitis present for which there was no explanation.

42. A man of 73 entered three hours after the onset of acute abdominal pain. The patient had a long history of stomach disturbances. He had also been under treatment for heart disease. Examination showed a sick old man with abdominal signs limited to the upper quadrant. There was fibrillation and ankle edema. Leukocytes numbered 13,000. Large amounts of free air were seen in the peritoneal cavity by roentgenogram. Operation under local anesthesia and ether revealed 2,200 cc. of turbid fluid in the abdomen and a large perforated anterior duodenal ulcer. The patient did very poorly postoperatively. Wound infection developed and was followed by evisceration, necessitating secondary suture. The patient died one month after operation.

43. A man of 42 entered seven hours after the onset of acute abdominal pain. On examination the patient did not appear particularly ill. The abdomen was tender throughout and silent, but only slightly distended. Leukocytes numbered 4,000. Free air was noted beneath both diaphragms. Under ether anesthesia the abdomen was opened and large quantities of turbid fluid aspirated. A 3 mm. perforation was found on the anterior wall of the stomach near the pylorus. This was sutured. The patient went into shock postoperatively and, in spite of transfusions, died. No autopsy was obtained.

44. A man of 65 entered eight hours after the onset of acute abdominal pain. The patient had been ill with chronic heart failure for two years, but had had no ulcer symptoms previous to a week before entry. Examination showed a thin old man with a rigid tender silent abdomen. Leukocytes numbered 17,000. Free air was seen under the right diaphragm by roentgenogram. Under local block anesthesia, an anterior gastric perforation, 3 mm. in diameter, was closed. There was very little fluid in the abdomen. Immediately postoperatively, the patient became extremely cyanotic and, in spite of oxygen therapy, died a few hours after operation. The cause of death was presumed to be heart failure. No autopsy was obtained.

45. A man of 57 entered 24 hours after the onset of acute abdominal pain. Language difficulty made the story unreliable. The patient had had a duodenal ulcer demonstrated by roentgenogram in this hospital. Examination showed that the patient did not appear severely ill. The abdomen was silent and tender but not spastic. Leukocytes numbered 4,050. Free air was demonstrated under the diaphragms by roentgenogram. Under cyclopropane anesthesia, a large amount of thin fluid containing fibrin was aspirated from the abdominal cavity. A prepyloric perforation was sutured. The patient's liver was enlarged and nodular. Two days postoperatively, the patient died.

Autopsy showed the peritoneal cavity to be clean and the ulcer well sutured. Death presumably was due to cirrhosis of the liver. A diagnosis of cirrhosis of the liver with ascites had been made also on the previous hospital entry. The patient had had a head injury just before the onset of symptoms of perforation, which, added to the language difficulty, confused the history.

46. A man of 58 entered 36 hours after onset of acute abdominal pain. The patient had a long history of stomach disorder for which he had had an operation ten years before (Billroth I). He also had active pulmonary tuberculosis for which he was undergoing treatment at the time of entry. Examination showed a sick man in mild shock with a silent tender abdomen. Leukocytes numbered 17,000. Free air was seen under the right diaphragm by roentgenogram. Operation, which was done under spinal anesthesia, after transfusion and 1,000 cc. of glucose, revealed a large amount of thin fluid in the abdomen. There was a marked amount of induration of the entire pyloric region of the stomach but only a tiny perforation. This was sutured. Postoperatively, although the perforation appeared to be handled satisfactorily, the patient became disoriented, attempted suicide. Extension of the pulmonary signs developed, the patient had a large hematemesis and died on the 19th postoperative day.

Autopsy confirmed the clinical findings and revealed the cause of death to be massive hemorrhage from an ulcer perforating into the head of the pancreas.

There were 32 deaths from all causes in this series of 265 cases of perforated ulcer, a mortality rate of 12 per cent. Since seventeen patients died following operation, the surgical mortality rate is 6.4 per cent. A similar mortality rate was reported by Graham[4] in a series of 125 cases in which operation was done. Graham emphasizes the preoperative preparation of patients and believes that all patients should be op-

erated upon. Of five patients who were not operated upon, all died.

If one is to pursue a delaying policy in the selected cases of perforated ulcer, careful clinical examination and re-examination must be employed. If the patient's condition becomes worse, after once having reached a level, one should operate at once, as in the following case:

47. A man of 54 entered two hours after the onset of acute abdominal pain. The patient had had symptoms suggestive of peptic ulcer for several months before entry. Symptoms had been worse the week before entry. Examination showed tenderness and spasm in the epigastrium. The patient had a slight fever. Leukocytes numbered 11,900. No free air was seen in the peritoneal cavity by roentgenogram.

The patient was observed the next few hours on the ward. Gastric suction was started and intravenous fluids were given. The tentative diagnosis was perforated ulcer which had sealed off. A few hours later the patient's temperature and pulse rose and reexamination showed increased abdominal signs. Operation was decided upon.

When the stomach was exposed, a considerable amount of fibrin was found on the anterior surface just proximal to the pylorus. A tiny perforation was seen in the middle of this fibrin plug. A moderate amount of free fluid was found in the peritoneal cavity which on culture showed only a yeast. The patient recovered satisfactorily. He died five years later from a gastric hemorrhage.

DISCUSSION

During the years from 1934 until 1948 the mortality rate from operations for acute perforation of peptic ulcer has been lowered in this hospital from 24.5 per cent to 6.5 per cent. This decrease is attributable mainly to a better trained house staff, a more general use of gastric suction, the use of antibiotics and chemotherapeutic agents and the careful preparation and selection of patients for operation.

In view of recent publications on the non-operative treatment of perforated peptic ulcers[5,6] an attempt has been made to analyze the deaths in this series to determine whether or not the outcome might have been altered by non-operative methods. Ten patients with proven perforations survived without operation while 15 died under similar management. Ten of the latter—they had been considered moribund at the time of entry—survived less than 24 hours. Of the remaining five, only one was considered for operation and he died following the administration of anesthetic. All 15 patients died of a generalized bacterial peritonitis. It is significant that of the ten patients who survived with non-operative treatment, four had previous perforations and the remaining six had long histories of ulcer symptoms. Although all of these patients had evidence of free air in the peritoneum, it is reasonable to assume that previous vaccination of the peritoneum and partial walling off of the peritoneal cavity with preformed adhesions were dominant factors in localizing the peritonitis and in facilitating recovery without operation. Three patients who were operated upon and found to have perforation sealed by a plastic exudate, survived without suture of the ulcer site.

It seems evident to us from these observations that the patient most likely to survive non-operative treatment is the patient who for one reason or another has peritoneal adhesions preventing general contamination of the peritoneal cavity following acute perforation. Such patients show clinical evidence of localized peritonitis and improve rapidly under observation. How one is to select such patients for conservative therapy is the problem.

In this study, 17 patients died following suture of the perforation. Of these, only four seem unwisely selected for operation. Possibly the course in these cases might have been altered by conservative management. However, this seems unlikely in view of a generalized peritonitis at the time of operation with no evidence of sealing of the ulcer.

The analysis of the deaths in this series seems to indicate that the patients least likely to survive an acute perforation are those who are suffering with an acute generalized bacterial peritonitis with an unsealed perforation whose general condition cannot be altered to permit operation. Only in exceptional circumstances do such patients recover on conservative management. On the other hand, patients who show no evidence of free air in the peritoneum, patients with previous perforations or a long-standing history of ulcer and localized peritonitis, may recover on conservative management. Non-operative treatment is indicated in such patients only when other considerations such as chronic alcoholism, pulmonary, renal or cardiac impairment contraindicate operation.

SUMMARY

1. Studies of 265 patients with perforated ulcer at the San Francisco Hospital reveal an overall mortality rate of 12 per cent with an operative mortality rate of 6.4 per cent.

2. Patients with perforated ulcer can survive without operation.

3. In the non-operative treatment of perforated ulcer, it would seem justifiable to delay operation in all those patients in whom peritonitis is apparently becoming localized and who seem to be improving clinically. One would be encouraged in this stand if no free air could be demonstrated in the peritoneal cavity by roentgenogram.

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Management of Acute Peritonitis

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ACUTE bacterial peritonitis has long maintained its position as one of the most dreaded of intra-abdominal lesions. In the past decade such important progress has been made in its therapeutic control that an integration of these developments may profitably be presented. In this discussion the assumed problem is the presence of an established, diffused, polymicrobic, enterogenous peritonitis. In general, acute peritonitis follows a pattern of three phases: an initial period of diffusion, lasting from a few hours to several days depending on its pathogenesis; a second period of established active peritonitis lasting seven to ten days; and, if recovery is to occur, a period of resolution. Residual abscess formation or mechanical intestinal obstruction may complicate this latter phase. Excepting complicating factors peculiar to the individual patient, the prognosis in acute peritonitis is dependent upon three factors: the lesion producing the peritoneal infection, the degree of sepsis, and the severity of the invariably associated, inhibitive type of intestinal obstruction.

One group of cases that can be used for measuring progress in the treatment of acute peritonitis is that of appendiceal origin. An excellent series for reference in this regard is that from the Cincinnati General Hospital, reported by Tashiro and Zinninger.[13] In the years 1915-1933, perforated appendicitis with peritonitis carried a mortality of 33.9 per cent. In the next five-year period (1934-1938, inclusive) this figure had been reduced to 17.2 per cent and in the five years 1939-1943 the rate had further declined to 13.8 per cent. The decline was attributable to improved surgical management of the individual cases, and to a vigorous lay educational campaign aimed at encouraging earlier medical attention and eliminating the use of cathartics. This latter approach is even today potentially the most effective means of controlling the mortality from peritonitis.

TREATMENT OF THE INDIVIDUAL CASE

After properly disposing of the problem of the primary lesion productive of acute peritonitis, the surgeon finds the subsequent phase of management determined by the existing peritonitis. In designing the regimen to be instituted, the three major elements of the peritonitis can be defined as follows: the systemic, the intestinal obstruction, and the septic factors.

SYSTEMIC DISTURBANCES

Perhaps the most promising future therapeutic possibilities in the sytemic phase of peritonitis are those indicated in the reports by Kay and Lockwood.[6,7] In their studies on dogs, the standard experimental situation was an appendiceal peritonitis produced by ligation of the base of the appendix and its mesentery, with a mortality of 41.7 per cent in a series of animals. In these animals, blood nonprotein nitrogen, total protein, chlorides, sodium and potassium levels were not significantly different in the survivors than in the animals that died. Blood taken during the crisis of peritonitis did not clot readily and when it did the thrombus was soft and non-retractile. In those instances of complete failure to clot the animals invariably died. There was spontaneous lysis of the clot within 48 hours in all animals that died, although some with this phenomenon did live. Associated with this increased proteolytic activity there was a prolongation of prothrombin time, and if this prolongation amounted to only a few seconds at the onset of the peritonitis the mortality was increased. If animals were fed trypsin preoperatively, the mortality was reduced to 6.6 per cent, by reason of the increased antiproteolytic activity of the serum of the treated animals. Because the proteolytic enzyme system of the serum is capable, unless inhibited, of quickly destroying the total fibrinogen of the body, the work of these investigators would indicate that disturbances of this system are potentially of great clinical importance in peritonitis.

In the hospital, active treatment of the systemic disturbances constitutes an essential phase of the management. The optimum position of the patient in bed is not yet agreed upon. The full Fowler's position has, however, been generally discarded as unphysiological, partly because of the manner in which it affects pulmonary and peripheral venous physiological processes. Further, the ability of Fowler's position to retard the development of upper abdominal abscess can be challenged. This challenge is based on the contention that the associated intestinal distention usually creates sufficient intra-abdominal pressure to exceed the effect of gravity and thereby neutralize the benefits of a semi-sitting position. It is our preference to have the bed flat, permitting the patient to roll, or be rolled, freely from side to side. This accomplishes, in principle, a horizontal axial circumrotation. Such a position, in conjunction with ankle exercises, qualitatively approximates many of the benefits of early ambulation. This alternate shifting of the dependent half of each lung to an opposite position in relation to the bronchial tree and to the heart, promotes bronchial and pulmonary venous drainage, as does the resultant full excursion of the diaphragm. If desired, the head end of the bed can be raised on blocks to improve vital capacity and secure the effect of gravity, but preserving freedom of mobility. An incidental beneficial effect may be that of shifting the kinked dilated loops of intestine, thereby promoting movement of fluid into the colon.

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Loss of the function of alimentation has frequently cost the life of a patient in whom the peritoneal infection would have healed if healing had not been handicapped by this starvation and fluid deprivation. Parenteral alimentation is a practical problem today, with most of the needed materials available. Fat, the one major element not yet generally available for intravenous use, is physiologically the least important. The average patient with peritonitis possesses adequate fat depots for the duration of the disease. Sound management requires a careful daily prescription of calculated amounts of water, sodium chloride, glucose, amino acids and vitamins, with less accurate but equally important efforts to replace blood proteins and erythrocytes by transfusion of whole blood, aimed at maintenance of a normal blood volume.

In the average hospital, water balance is best maintained by study of the daily urine output. If urine specific gravity is over 1.015, an output of 1000 cc. is ordinarily adequate. The most difficult phase has to do with the dose of sodium, partly because our understanding of sodium need in general is in a state of revision, and partly because it is being recognized that sodium chloride retention occurs in peritonitis. A daily dose of 9-12 gm. of sodium chloride would seem to be the maximum advisable in the average case even with indwelling gastric suction, except for patients with perforated peptic ulcer, whose hyperchlorhydria conditions a precocious dechlorination. It appears that the usual error is to give too much sodium, especially in the older patients. One approach to the problem is to favor glucose in water, and to add sodium upon the appearance of diuresis. This is based upon the fact that the interstitial fluid pool of the body requires sodium to hold its water, and that diuresis is indicative of the dumping of water because of insufficient sodium to hold it in this pool. Such a diuresis, therefore, is evidence of sodium want. To build the pool volume back to normal requires both sodium chloride and water. Carbohydrate administration, as 5 or 10 per cent aqueous solution of glucose, spares protein, reduces ketosis, and reduces the caloric deficit. Too rapid administration results in glycosuria and diuresis. Ten per cent glucose solution is often preferable, given slowly the first half hour, and then given at a rate so that from 2 to 2½ hours is required for the administration of 1000 cc. The nitrogen deficiency in peritonitis can now be effectively influenced by the administration of 5 per cent amino acid solutions, preferably with 5 per cent glucose. Very special precautions are required to avoid reactions. A liter of this solution daily, with adequate complementary glucose, is a specific attack on the problem of negative nitrogen balance, most easily visualized by the fatty liver, with its multitude of attendant hepatic dysfunctions. In the vitamin phase of therapy, a daily parenteral dose of crude liver extract gives coverage of an extensive list of these elements. Thiamine, riboflavin, nicotinamide, and ascorbic acid are commonly considered to be desirable additions if excessive doses are avoided.

INTESTINAL OBSTRUCTION

In addition to the loss of nutritional intake, the patient with peritonitis is subjected to most of the disturbances of low simple intestinal obstruction, by reason of the inhibitive ileus. Among these disturbances the factor of distention usually is the most tangible at the bedside. In the experimental laboratory, distention has been proven to be an extremely important element in the pathologic changes of intestinal obstruction. Perhaps the most notable early investigation of the effects of distention was by Van Zwalenburg of Riverside.[14] Herrin and Meek[5] have shown that distention of the jejunum without obstruction of it will produce dechlorination, dehydration, and death almost as regularly as will obstruction of it. In treating distention the surgeon cannot control the hypersecretion and decreased absorption producing excessive intraluminal fluid. However, the increased intestinal volume is to a large degree dependent on the accumulation of gas. Because most intestinal gases do not exist in the atmosphere, they can be absorbed by the blood and be passed off by the lungs. Because the atmosphere is largely nitrogen, this particular gas cannot be disposed of in this way, and, in effect, swallowed air, largely nitrogen, becomes a foreign body in the intestinal tract. An indwelling gastric catheter, with suction, as first suggested by Ward of San Francisco,[15] will prevent this swallowed air from entering the intestinal tract.

Various devices to provide suction, and tube modifications to secure gastric, duodenal, jejunal or ileal levels of drainage have been developed for removing gas and accumulated secretions. These devices are of very great importance. Instead of waiting until distention develops, the surgeon should use gastric or duodenal suction as soon as a diagnosis of peritonitis is made. If distention of significant degree is present, intubation and suction may be required at lower intestinal levels. It should be indicated that when peritonitis heals, deflation will occur spontaneously. Distention should never be treated with peristaltic stimulants, which may be lethal.

All of the foregoing considerations focus on the treatment of the ileus by mechanical decompression of the orad segment of the gastro-intestinal tract, and attempt to emphasize the great value of such measures.

TREATMENT OF THE PERITONEAL INFECTION

Until recently, administration of Cl. Welchii antitoxin and the transfusion of blood from individuals convalescing from enterogenous peritonitis constituted the only direct therapeutic attack on the peritoneal infection. With the use of the sulfone compounds in peritonitis a decrease in the mortality rate was generally observed. Tashiro and Zinninger[13] reported a mortality of 11.3 per cent when these drugs were used systemically in general peritonitis, as compared with 18.8 per cent in a comparable group of patients who did not receive them.

The value of penicillin in acute appendiceal peritonitis was indicated in the report of Crile.[1] In his series of 50 cases from a Naval hospital, there was only one death and that was due to mesenteric thrombosis. These patients were treated with doses of 100,000 units of penicillin every two hours, and it was concluded that the resultant high concentrations were adequate to permit a positive effect on the coccal organisms in spite of the inhibiting effect of the penicillinase produced by the Escherichia coli. No comparable series in which streptomycin was used has been reported as yet.

In the laboratory field, using Gram-negative bacilli, it has been shown that an average lethal dose of their endotoxins could be raised two times if the animals were protected with crystalline penicillin, and eight times using mixed penicillin.[8] This endotoxin neutralizing effect, it should be emphasized, is independent of any bactericidal activity. Another significant observation regarding penicillin relates to bactericidal doses in vitro.[2] For a particular organism, gradually increasing concentrations determine "a maximally effective concentration which varies between two and ten times the 'sensitivity' level of the organism as ordinarily defined." Even a 20,000 fold increase does not intensify this effect, and, in not a few strains the level of activity is reduced by the higher concentrations. Up to the present time in vitro laboratory studies have not duplicated the problem presented by peritonitis due to the complex situation wherein susceptible Gram-positive cocci and penicillinase-producing Gram-negative bacilli exist in symbiosis.

In animals with peritonitis the beneficial effects of penicillin have been shown.[3,4] The clinical and laboratory observations have failed to establish an optimal dose. Because of the need for conservation of penicillin at the time of its introduction, most clinical studies of its use in various infections were aimed at establishing the minimum effective dose. In this regard, the revisions necessary, and the ultimate results in subacute bacterial endocarditis should be recalled. There is need for determination of the necessary dosage of penicillin for production of maximum effects in acute peritonitis.

Discovery of streptomycin revealed an antibiotic with many features surpassing penicillin for therapy of acute peritonitis, particularly because of its activity against Gram-negative bacilli. It is worth emphasizing that streptomycin possesses a wide anti-bacterial spectrum, including many strains of Gram-positive cocci, some of which are not sensitive to penicillin. Its higher toxicity and the quite rapid development of resistance in susceptible strains constitute its main deficiencies. Its definite value in experimental appendiceal peritonitis is well established.[3,9] The effects of streptomycin and penicillin are cumulative upon organisms susceptible to each.[10] In the treatment of acute infections the optimum therapeutic dose of streptomycin seems fairly well established at 0.5 gm. every four hours. This dosage in conjunction with large doses of penicillin, such as 100,000 units of mixed penicillin every two or three hours, would seem to be the most desirable antibiotic therapy available at present. A recent report on polymyxin indicates the existence of a new antibiotic substance with very active streptomycin-like activity against Gram-negative bacilli, and without the rapid development of resistant or "drug fast" strains.[12]

USE OF PENICILLIN ALONE

Clinical investigation of the value of penicillin as the only antibiotic factor in a group of patients representing all ages, and suffering from appendiceal peritonitis, has seemed desirable. Partly, this was due to the numerous objections to the sulfa drugs, and partly to the need for such a study in order to create a yardstick for comparison in any subsequent study of the clinical results with streptomycin. To this end a routine was established for the management of perforated appendicitis in one of the surgical divisions at the Los Angeles County General Hospital. The major features consisted of routine removal of the appendix through a McBurney incision, closure of the peritoneum without drainage, and the intramuscular administration of 100,000 units of penicillin every three hours, or with the same dose, but half given intramuscularly and half subcutaneously.[11] The ancillary management was carried out as described in the previous paragraphs. In one period there were 48 cases of acute perforated appendicitis and peritonitis with two deaths, neither of which was directly attributable to peritonitis. The same management, except that surgical operation was withheld, was used in 13 cases of appendiceal abscess, with no deaths and no operations for drainage. The majority of the operations done were carried out by the resident staff. There were no instances of subphrenic abscess, fecal fistula, or mechanical intestinal obstruction. This mortality of 3.3 per cent would seem to justify the belief that peritonitis can be quite successfully controlled by the application of an adequate program based on present knowledge.

SUMMARY

Acute bacterial peritonitis of enteric origin presents a clinical problem with numerous important disturbances secondary to the peritoneal sepsis. Proper management entails an appreciation of each of these, and an approximation of their correction whenever possible. A somewhat standard plan of treatment has been presented.

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The Role of Tissue Permeability With Particular Reference To the Blood-Brain Barrier in Diseases of the Central Nervous System

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THE attention of certain of my associates and myself has been directed both experimentally and clinically for several years to the possibility that permeability plays a role in disease processes of the central nervous system. We have been particularly interested in the blood-brain barrier and have developed methods for studying the permeability of this neurophysiological mechanism.

We have been able to show that the locus of this barrier resides, as Spatz[13] postulated, in the endothelial cells lining the walls of the cerebrovascular tree. Using the supravital dyes, Brilliant Vital Red and Trypan Red,[2] which uniquely stain these cells and which do not pass beyond the blood vessels to gain entrance into the nerve tissue proper, we have been able to lower the permeability of the blood-brain barrier and to prevent abnormal increases in the permeability of this barrier such as occur in many diseases of the central nervous system and which we have been able to produce in certain instances under controlled conditions in the experimental laboratory.

The neurophysiologic role of the blood-brain barrier is presumably fundamental in maintaining the homeostasis and conditions for normal metabolism within the central nervous system. The barrier also plays an important role in protecting the brain in various toxic conditions. For example, the barrier normally is impermeable to such electro-negative bacterial toxins as tetanus, diphtheria, botulinus and staphylococcus and such chemical agents as thiocyanates, neoarsphenamine, iodides and bromides.[10]

Studies on the blood-brain barrier indicate that practically all disease processes of the central nervous system tend to break the barrier down, that is, abnormally increase the permeability of the barrier. The results of the numerous studies[11] along this line may be listed in the following categories:

1. *Inflammatory Processes*
   - Meningitis
   - Encephalitis
   - Virus Infections
   - Abscess
   - Injury
2. *Toxic Processes*
   - Eclampsia
   - Acute Alcoholism
   - Theophyllin
   - Urotropin
   - Potassium Bromide
   - Urea
   - Bile Salts
   - Sodium Salicylate
3. *Physiologic Conditions*
   - High and low pH
   - High and low osmotic pressure
   - Menstruation
4. *Other Diseases of the Central Nervous System*
   - Tumors
   - Gliosis
5. *Tests and Surgical Procedures*
   - Craniotomy
   - Pneumoencephalogram
   - Lumbar puncture with forced drainage of cerebrospinal fluid

From the Divisions of Neurology and of Neurosurgery, the Electroencephalographic Laboratory of the University of California Medical School and the Spectrographic Laboratory of the University of California Medical School. These studies were made possible by grants from the Christine Breon Fund.

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Although the techniques and methods used in the majority of these studies may be criticized, the results in many studies and especially in those which have employed dyes, indicate that almost any disturbance within the central nervous system is associated with an increase in the permeability of the blood-brain barrier.

Our own studies have been directed along the following lines: to study the role of permeability in

1. Toxic diseases of the central nervous system.
2. Degenerative diseases of the central nervous system of possible toxic origin.
3. Cerebral concussion and other post-traumatic conditions.
4. Convulsive states.
5. Electroshock therapy.
6. Cerebro-vascular disorders.

Both experimental and clinical studies have been performed along these various lines. The traumatic and electroshock studies, for example, have been largely experimental, while the degenerative studies have been largely clinical. In all instances, however, the fundamental experimental observation that the permeability of the blood-brain barrier could be lowered by the supravital dyes, Brilliant Vital Red[1] and Trypan Red[2] has been used as a mechanism to alter the permeability in each condition studied and to test the relationship between permeability and other findings characteristic of the condition. For example, in using triphenyl phosphite as a convulsive agent in experimental epilepsy[3] we found that this compound was hydrolyzed readily in vivo and that two effects resulted from its breakdown products. The phenol fraction produced early convulsive effects at the cord level and the phosphorous acid fraction was selectively and preferentially absorbed by the gray matter of the central nervous system and caused late degenerative changes in the nervous system similar to such other esters of phosphorous acid as triorthocresyl phosphite, which produces a combined system degeneration of the spinal cord, and triorthocresyl phosphate, the contaminant responsible for the degenerative changes in cases of Jamaica ginger paralysis. If the animals were previously stained with Brilliant Vital Red, these toxic effects could be prevented. This illustrates our use of the dyes in toxic conditions of the central nervous system.

Our interest in the degenerative diseases of the central nervous system was stimulated by the concept that certain of these unexplained conditions might have a toxic origin. For example, this theory has been postulated for amyotrophic lateral sclerosis. Since the supravital dyes can be used with safety in man, we felt justified in trying them in these otherwise hopeless conditions with which we are so frequently confronted in neurologic practice. Such studies have been done without promises and only after a frank discussion of the situation with the patient and his family which would assure us of their cooperation in the prolonged follow-up that is essential in these conditions. Aside from testing the value of the dye therapy in these cases, we hoped that we might begin to sort out the large group of degenerative diseases and segregate those of toxic origin from the rest of the group.

Reference will be made only to one member of this group—amyotrophic lateral sclerosis.[4] Our results have been classified on a four-point scale:

1. No objective effect but possible subjective improvement.
2. Diminution of fasciculation.
3. Suggestive slowing of disease.
4. Process arrested and possible improvement in strength and weight.

On this basis, fasciculations were diminished in the majority, progression of the disease process was suggestively slowed in nearly 50 per cent and about one patient in six obtained an apparent arrest or even some improvement.

Although no final conclusions may be drawn from such data, the relationship between treatment and improvement in several patients appeared more than coincidental, especially in those patients in whom a recurrence of the disease process, following a discontinuance of the treatment, was again modified when adequate dye therapy was resumed. We have felt that the results were sufficiently encouraging to warrant further trial. Tentatively the same may be said for progressive muscular atrophy and progressive muscular dystrophy. Because of the variable and remissive course, characteristic of multiple sclerosis, it is impossible to arrive at any early conclusions in this condition. Our experience in other, more rare diseases of the central nervous system is too limited to permit any conclusions. Final conclusions as to the value of the dye therapy in these conditions and as to the significance of the results in establishing a toxic origin of them must await further trial and experience.

Our interest in cerebral concussion was stimulated by the concept that the maximal effect of a transmitted concussive blow might be expected at those points at which abrupt changes occur in the structure and density of the brain.[5,6] Shearing forces are known to produce their greatest effect at such junction points. Considering the anatomy of the brain, one would not expect major changes between cellular and extracellular elements, that is, along the cell membranes of the relatively homogeneous masses of the cerebral cortex. Where the cellular masses of the brain join other structures of different histological character, which are relatively large and fixed, such as the ependymal lining of the ventricular spaces and especially where the cellular masses of the brain make contact with their supporting vascular tree, one might expect greater shearing forces and neurophysiological changes. Disrupting effects at this latter point might be reflected in changes of vascular permeability, perivascular edema and nutritional alterations in the neighborhood effecting cerebral metabolism. Depending upon its severity and duration, neurophysiologic changes and even irreversible, degenerative changes might be produced. The perivas-

cular pathological changes described by Scheinker and Evans,[12,9] in more severe traumatic lesions of the brain would be in keeping with this hypothesis.

With this concept in mind, we have studied the effect of concussion on the vascular structure of the brain and have done so in experiments aimed to give us information on the permeability of the blood-brain barrier. The studies involved determinations of the distribution of cocaine by spectrophotometric methods in the brain and blood following the intravenous administration of this drug in control and traumatic groups of cats. As intimated, the object of these experiments was to determine whether or not alterations in the concentration of cocaine occurred in the central nervous system following cerebral concussion, which might reflect permeability effects of possible neurophysiologic and etiologic importance in the post-concussional state and post-traumatic head conditions.

Significant rises in the concentration of cocaine were found in the cerebral cortex after concussion without appreciable alterations in the blood concentration levels. These results indicate that cerebral concussion increases the permeability of the blood-brain barrier. Similar studies following preliminary injections of Trypan Red showed concentrations of cocaine in the post-concussional cortex which were equal to or lower than the corresponding control values, while again the blood concentration levels remained the same. It was concluded that Trypan Red effectively counteracted the permeability effect of cerebral concussion on the blood-brain barrier. It is also of interest in these studies that while approximately 80 per cent of the cats showed a cerebral dysrhythmia by electroencephalography three days after cerebral concussion, following preliminary Trypan Red injections the dysrhythmia either did not appear or appeared only in minor degree three days after traumatization. Since Trypan Red appears to counteract both the increase in permeability of the blood-brain barrier and the cerebral dysrhythmia associated with cerebral concussion, this dye may prove of practical value in determining the possible relationship between these neurophysiologic phenomena and the clinical symptoms characteristic of the post-concussional state. Inasmuch as Trypan Red may be used with safety in man, such therapeutic possibilities appeared worthy of exploration. Preliminary clinical studies, which are at present under way, suggest that this agent may have some beneficial effect on the post-concussive state.

Our interest in the use of the supravital dyes in the convulsive states was initiated by the discovery of Cobb and his co-workers[8] that Brilliant Vital Red would protect in both toxic epilepsy under controlled experimental conditions and also in human convulsive states. We have confirmed the observations of Cobb in both experimental and human epilepsy[1] and have continued to use this method of treatment as an adjunct to other anti-convulsive therapy when more routine methods have not proven adequate to control the convulsive state. Although not as potent as some of the modern anti-convulsive drugs now available, it is a valuable agent in those patients not fully protected by the usual methods, since it can be used in conjunction with them. We have also found that Trypan Red[2] is, in general, as effective as Brilliant Vital Red and because of its lower solubility and the fact that it is excreted more slowly than Brilliant Vital Red, it has proven of more practical value in actual practice.

The implications of the effectiveness of the supravital dyes in epilepsy are interesting and important. Why should an agent which alters the permeability of the blood-brain barrier and which does not itself gain entrance to the nerve tissue proper, have any effect on the convulsive state? The answer must be sought in the effect of the blood-brain barrier upon the physiological and biochemical state of the brain and consequently its effect in modifying the reactivity of the brain. When one considers the basic mechanisms known to modify the convulsive state, such as the acid-base balance and water balance of the central nervous system, it becomes apparent that many mechanisms which lower the permeability of tissue also afford protection in the convulsive states and, vice versa, that factors which increase permeability also increase convulsive susceptibility. Although the alteration of permeability in itself is presumably of the greatest importance in epilepsy induced by drugs, it is conceivable that some other changes associated with this alteration may be the precipitating factor in human epilepsy. Numerous complex physiologic and biochemical changes are associated with an alteration of the semipermeable characteristics of tissue membranes, and since these changes occur together, it is not possible to say that any single factor or combinations of factors is responsible for any resulting physiological effect. It seems likely that the convulsive state is a result of the whole complex of changes, that is, the changes associated with increased permeability in cortical tissue cause a more unstable and irritable state which, in turn, is characterized by an increased susceptibility to convulsions. As has been pointed out, those mechanisms, which are known to increase the permeability of tissue, such as alkalosis, hydration, anoxemia and inflammatory changes, are also known to lower the convulsive threshold. As a single mechanism of fundamental neurophysiologic importance in determining cellular nutrition and reactivity, permeability, or rather the complex of changes associated with alterations of permeability, offers an attractive hypothesis for the numerous, and otherwise unrelated, factors known to be of importance in modifying convulsive reactivity.

More recent investigations, possibly related to our earlier studies on the convulsive states, have been conducted in an attempt to elucidate the neurophysiologic basis of electroshock therapy.[7] Experimental studies with electroshock have been disappointing in that they have failed to explain the basis for the beneficial effects of this form of therapy in psychiatric conditions. Considering the anatomy of the vascular

tree of the brain and what is known concerning the transmission of electrical currents through tissues, one might postulate that a high percentage of the current traversing the brain would concentrate on and be transmitted along the vascular tree of the brain or in its blood stream. According to this concept, only as the current concentrated on the vascular tree in the cortex or escaped into the deep subcortical portions of the brain from the deeper blood vessels would the brain be stimulated. Since the effect on the vascular tree might be reflected in changes of the semipermeable characteristics of the membranes composing the blood vessel walls, as indeed has been suggested by neuropathological studies, we have initiated studies using techniques previously reported for measuring alterations in the permeability of the blood-brain barrier. The permeability of the blood-brain barrier was therefore studied in the same manner as mentioned previously, both before and after a series of electroshock treatments in cats. It was found, as suspected, that electroshock therapy did appreciably increase the permeability of the blood-brain barrier and that this effect persisted for days in contradistinction to the fleeting change of permeability which occurs in nerve tissue after its electrical stimulation. In another series of experiments, in which the cats were injected with Trypan Red before the series of electroshock treatments were given, it was found that the dye prevented the permeability changes of the first series of experiments. In these same experiments, a generalized cerebral dysrhythmia was obtained by electroencephalography in the initial shock experiments but was either not obtained or only slightly so in the second series of experiments after Trypan Red was used.

Since Trypan Red appears to counteract both the increase in permeability of the blood-brain barrier and the cerebral dysrhythmia associated with electroshock therapy, one wonders if it might not also counteract the beneficial effect of such therapy in psychiatric conditions. Although the practical difficulties of clinical investigation along these lines are obvious, suitable methods are being sought to test further the possible relationship between these persistent neurophysiologic phenomena and the beneficial effects of electroshock therapy.

An increase in permeability presumably occurs with the abnormal vasodilatation such as is associated with headaches of vascular origin, such as migraine and histamine headaches. This factor may account for the pipe-stem arteries, prolongation of symptoms and ineffectiveness of ergotamine tartrate when given late in an attack of migraine, for example. Again, this same permeability mechanism is presumably involved in conditions associated with perivascular disease, such as encephalitis lethargica, anterior poliomyelitis, the demyelinating diseases and the more severe post-traumatic head conditions already mentioned. Since such perivascular disease probably plays at least a secondary role in the pathological physiology of these conditions, supravital dye therapy, if it diminished or controlled this effect, might prove of some therapeutic value in them. Certain possibilities along these lines are now being investigated and it is hoped will be the subject of more specific reports at a later date.

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The Management of Acute and Chronic Pulmonary Abscess

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PULMONARY abscess is a serious and unpredictable disease. While it has been estimated that from 25 to 35 per cent of patients become well spontaneously, the mortality has been from 30 to 50 per cent in most series of prior years.[1] We have long been opposed to the tendency of many physicians to separate the treatment of lung abscess into a medical phase and a surgical phase. In the not-too-far-distant past it was the custom to set a time limit, usually from six weeks to three months, for the period of purely "medical treatment." If the abscess was not cured by then, the case automatically became surgical. The effects of treating such a serious disease by this routine have been amply reflected in the appalling mortality statistics just quoted. There is now greater appreciation of the fact that pulmonary abscess is a suppurative disease and that because of this, surgical intervention becomes an ever-present possibility. The best results are obtained by the physician and thoracic surgeon working as a close team from the onset of illness. Observation is not treatment. Definitive therapy should be started at once. Radical change in treatment should be accepted by both physician and patient as an inherent part of the therapeutic regimen in this disease.

DIAGNOSIS

It should not be difficult to make a diagnosis of pulmonary abscess. While in a few cases the abscess is undoubtedly due to septic emboli, in the great majority it comes from aspiration, with blockage of a bronchopulmonary segment and distal suppuration. Pulmonary abscesses often follow operations around the mouth, nose, or face. In a majority of the few cases in which there was no such operation prior to the development of abscess, poor oral hygiene is evident.

Many patients show prodromal symptoms of generalized malaise, fever, and fairly localized thoracic pain. This will be followed within a few hours or a few days by sudden or increasing expectoration of large amounts of purulent sputum which layers out on standing. The sputum is not necessarily foul, but is frequently so at the onset. Roentgen studies in the frontal and lateral views will almost always clinch the diagnosis. It must be remembered that a fluid level or cavitation may not be seen on the roentgenogram. This usually means that the abscess has not yet emptied itself sufficiently.

ACUTE ABSCESS

The management of acute pulmonary abscess encompasses general hygienic care, the use of antibiotics and chemotherapy, and the promotion and maintenance of adequate drainage. Careful attention to the therapeutic details described in the following text has resulted in cure in approximately three out of four cases, without resort to surgery. In the other 25 per cent, surgical drainage has been necessary.

The intake of fluids, calories, vitamins and proteins should be adequate. Any deficiencies in oral intake should be made up by the parenteral route. The patients often develop considerable anemia. Iron mixtures may suffice, but if the hemoglobin falls to 70 per cent or below, whole blood transfusions are indicated.

The sulfa drugs and penicillin have been widely used in the treatment of pulmonary abscess. Probably their biggest contribution is in the prevention of invasive infection. The ancillary nature of this therapy must be emphasized. There has been no marked increase in the non-surgical incidence of cure since the beginning of widespread use of sulfa compounds and penicillin. There is some evidence to show that a combination of both drugs may be more efficacious than either one used alone.[5] Penicillin is administered by the aerosol and intramuscular routes. Drug therapy can be overdone, however, and is completely ineffective if the abscess does not drain properly. An abscess cavity may be temporarily sterilized, but it will not heal if a necrotic slough remains.

The most important single factor in cure is to establish adequate drainage. This is characteristic of an abscess in any portion of the body. Because all pulmonary abscesses possess a bronchial connection, it is possible that so-called internal drainage may suffice.

Adequate internal drainage is best initiated and maintained by modified postural drainage and by bronchoscopic aspiration. The type of postural drainage to be used must be individualized. In general, the patient should be instructed to assume the position which makes him cough most, four or five times during the day. Cough is a natural defense mechanism in raising secretions and is a good index as to whether or not postural drainage is being done in the most efficient position. The usual position of postural drainage with the patient hanging over the bed almost straight down from the hips may be harmful if the abscess is in the middle or upper lobes. The bronchoscope is an invaluable means of improving internal drainage. In the past bronchoscopy has been used far too infrequently during the acute phase of the abscess. Bronchoscopy should be one of the earliest therapeutic procedures employed. It has been stated that many patients are too sick to be subjected to bronchoscopy. Rather it should

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be said that they are too ill not to be bronchoscoped. There are many who still are unconvinced as to the value of bronchoscopy. Such physicians either have not noted the benefit of an efficiently performed bronchoscopy, or they have been swayed by the operator's enthusiasm and allowed repeated bronchoscopies to be performed without appreciable improvement in the patient's condition. This cannot be held against the method, but is an indictment of the bronchoscopist's judgment. The bronchoscope is not an infallible instrument. One must not try to do the impossible with repeated aspirations if progressive clinical and roentgenologically demonstrable improvement does not ensue.

In brief, the bronchoscopist can be depended upon to do the following tasks: (1) Make an occasional diagnosis of unsuspected foreign body or neoplasm as the causative agent of the abscess; (2) remove obstructing secretions from the main and secondary bronchi; (3) elicit selective cough with further evacuation of secretions from the infected lobe; (4) shrink the congested edematous mucosa which in itself can cause visible obstruction of the bronchial airway; (5) pass long curved aspirators into the smaller bronchi of the diseased pulmonary segment and, rarely, directly into the abscess cavity.

In favorable cases the effects of bronchoscopy can be seen within a few days after the first aspiration. In many cases a second or third bronchoscopy at from five to seven-day intervals may be indicated. If, within 14 days after these procedures have been performed, there is still question as to the trend of the illness, it is unlikely that improvement has occurred and the type of treatment should be changed.

Once the patient with pulmonary abscess has come under the physician's care, improvement must be prompt and progressive or surgical operation should be undertaken. The improvement must be both clinical and roentgenologically observable. No abscess is doing well which remains unchanged on the roentgenograms for two or three weeks at a time, even though there has been amelioration of symptoms. Undoubted clinical improvement is manifested by decrease in the cough, reduction in the amount of sputum, a change in the character and odor of the sputum, a reduction in the fever, and an increased sense of well-being on the part of the patient. Should the fever continue at its previous level or should the secretions remain purulent and foul it is certain that drainage is ineffective. Improvement from the roentgen standpoint is manifested by loss of fluid levels, a decrease in the amount of surrounding pneumonitis, and progressive decrease in the size of the abscess cavity. The cavity which remains stationary or increases in size, particularly if there are associated symptoms of impaired drainage, is sufficient indication for surgical intervention.

The decision to initiate surgical intervention usually can and should be made well within six weeks of the onset of the disease. Brisk hemorrhage is an indication for prompt surgical drainage at any time it occurs.

Two pitfalls should be guarded against before operative drainage of a cavity is decided upon. Occasionally an abscess may develop which is merely an acute infective episode associated with chronic bronchiectasis. In such cases the patient does poorly following surgical drainage. A carefully taken history will help to avoid this mistake. Likewise a suppurating pulmonary cyst should not be drained unless the severity of the infection forces this action. Because of their mucosal lining, these cysts will not heal.

Most abscesses can be drained by a one-stage procedure. Since nearly all abscesses are on a pleural surface, adhesions rapidly form between the thoracic wall and the lung. These frequently cover a small area and accurate roentgen localization by means of fluoroscopy, frontal stereoscopic and lateral films is necessary prior to operation. The anesthetic may be either a combination of regional and local block with procaine or nitrous oxide and oxygen. A slightly curved incision is made and sections of one or two ribs together with the intervening intercostal bundle are removed. If the pleural space is not obliterated, an irritating pack of half-strength tincture of iodine or 1-1000 acriflavine solution should be placed against the parietal pleura as the first stage and left in place for approximately seven days. It is wise to recheck with roentgenograms after the first operation to be sure that the abscess is being approached properly. The abscess should be opened with a cautery and the contents evacuated simultaneously with suction. Bleeding is controlled by cautery or by suture-ligature. The cavity is packed lightly with gauze and repacked as necessary until healing takes place. In most instances where destruction of lung has not been too great the abscess cavity will gradually become obliterated by resolution and by re-expansion of the remaining lung. If the healing process is delayed much beyond six weeks and the cavity is clean, some type of filling with free fat grafts or with a pedicled muscle flap is advisable.

In rare instances severe hemorrhage may dictate a one-stage procedure, even in the absence of pleural adhesions. In such cases the area to be cauterized is encircled by mattress sutures which hold the lung in apposition to the chest wall.

Sudden thoracic pain, dyspnea, increased fever, and profound toxemia herald the sudden rupture of a pulmonary abscess into the pleural cavity. In our opinion this serious complication constitutes a surgical emergency. Any temporizing with repeated aspirations and the injection of sulfa drugs or antibiotics is almost certain to end disastrously. Likewise, closed intercostal drainage in this type of acute empyema is unsatisfactory in the extreme. Such treatments frequently result in spreading anaerobic cellulitis or fascitis of the thoracic wall and the mortality then is very high. The treatment of choice is to ignore the abscess for the time being and to open the pleural cavity widely by a long posterior resection of the 8th or 9th rib.[3] Rapid evacuation of infected contents is accomplished and multiple Pen-

rose drains are introduced into the pleural cavity, supported by a large pack. If, and when, the lung re-expands the abscess can be dealt with as necessary at a later date.

CHRONIC PULMONARY ABSCESS

It may be difficult to distinguish accurately between acute and chronic abscess. Pathologically speaking, chronicity in infection means the formation of mature scar tissue and the predominance of round cell infiltration over polymorphonuclear invasion. In pulmonary abscess chronicity is characterized by increased pulmonary destruction and fibrosis of the parenchyma with extensive pneumonitis and bronchiectasis. Some of these changes may occur as early as six weeks after the onset if treatment has failed of undoubted improvement or of cure.

Attention to general hygienic measures is more important in chronic than in acute pulmonary abscess. In particular, severe anemia and protein deficiency inevitably will develop unless proper preventive measures are taken.

In the treatment of chronic abscess bronchoscopy always should be performed for diagnostic purposes and to improve drainage. In rare instances one, or several, bronchoscopies may effect a cure.[4] If the cavity does not have thick walls and if the surrounding parenchyma seems normal, external drainage may be considered. If, however, the area of infection casts a dense shadow with multiple small areas of excavation, if the surrounding parenchyma seems contracted, or if the abscess is thick-walled or unduly large, external drainage probably will fail. As a general rule, the more chronic the abscess the less the chance of cure by drainage procedures. In any event bronchograms should be made before external drainage is decided upon. In the presence of associated bronchiectasis or of bronchial obstruction, external drainage will not succeed.

Signs of chronicity may develop in an abscess which has been inadequately drained. Fistulae will remain widely patent and develop indurated orifices; heavy purulent discharge will persist. While we cannot prove it statistically we have the impression that a true septic infarct which cavitates is less likely to heal following surgical drainage than is an abscess which results from aspiration. In the former instance it may be that the surrounding parenchyma has a permanently poor blood supply which is a factor in the development of chronicity. Occasionally one may be tempted to perform secondary drainage procedures on an abscess which is not "clearing up" properly. Those procedures are frequently unsuccessful because of the underlying irreversible pulmonary damage. In fact, Churchill has failed to cure any recurrent abscess by re-establishing drainage.[2,6] Further drainage may be indicated if a secondary acute abscess develops as an extension of the original process.

It has become increasingly evident that many cases of chronic pulmonary abscess should be treated primarily by pulmonary resection rather than by external drainage. Lobectomy, performed in the modern manner, carries far less hazard than the external drainage of a chronic abscess. If preoperative survey shows an entire lobe to be damaged, total lobectomy should be performed. If the disease is definitely localized, segmental lobectomy may be indicated. The lingular division of the left upper lobe and the superior (dorsal, apical) divisions of the lower lobes lend themselves particularly well to segmental resection. If all lobes on one side are involved, total pneumonectomy by individual ligation is infinitely preferable to attempted cautery penumonectomy. Even though external drainage has been attempted and has failed, resection still can be accomplished. The hazard, however, is increased somewhat because of the greater chance for intrapleural and wound infection. In performing an operation of this type, separate instruments should be used to free up the draining sinus, excise the epithelial portion, invert the remainder and close the overlying skin. The chest is then opened through a separate incision, the operator using clean gowns, gloves, and instruments.

SUMMARY

The hazards of pulmonary abscess are discussed and the necessity for early definitive therapy is stressed.

The treatment of acute abscess is outlined, including provisions for general hygienic care, the role of chemotherapy and the supreme importance of adequate drainage.

The role of bronchoscopy is emphasized in establishing and maintaining curative "internal drainage."

With proper attention to the above details approximately 75 per cent of patients with acute pulmonary abscess can be cured without resort to surgical operation.

The indications for external surgical drainage of acute abscess are listed.

The irreversible pulmonary changes associated with chronic pulmonary abscess are described.

The surgical problem in chronic abscess is contrasted with that in acute abscess.

The value of pulmonary resection in the treatment of chronic pulmonary abscess is stressed.

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Analysis of Fatal Cases of Poliomyelitis

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POLIOMYELITIS has been a problem among military personnel since the expansion of the Army. During the period 1940-1946, there was a total of 1,654 cases with 286 deaths. (Table 1.)

Poliomyelitis in its etiological, diagnostic and therapeutic aspects has been covered in the literature[7,12,13] and this paper is concerned with the statistical analysis of data available in 149 fatal cases from the United States Army hospitals† during 1944-1945. Reports of additional cases are available but are not included because of incomplete clinical records.

INCIDENCE

The incidence and mortality among military personnel compared with reports from the United States Public Health Service for the general population is shown in Table 1. The incidence in the Army is lower, as would be expected, since different age groups are involved. The mortality among military personnel is higher, the average for the Army for the period 1940-1945 being 17 per cent, while that for the general population was 9 per cent. This would indicate that the disease has a high mortality among adults of military age.

TABLE 1.—*Incidence of Poliomyelitis in U. S. Army Compared with the United States*

Year	Number Cases U.S. Army	Number Cases United States	Deaths U.S. Army	Deaths United States	Per Cent Mortality U.S. Army	Per Cent Mortality United States
1940	8 (1:42,000) *	9,826‡ (1:14,000)	2	1,026	25%	10%
1941	45 (1:30,000)	9,086 (1:14,000)	7	807	16%	9%
1942	62 (1:52,000)	4,033 (1:32,000)	5	561	8%	14%
1943	248 (1:28,000)	12,449 (1:12,000)	49	1,151	20%	9%
1944	350 (1:22,000)	19,029 (1:6,800)	59	1,361	17%	7%
1945	680 (1:11,000)	13,619 (1:10,000)	129	1,186	19%	9%
1946	261 (1:8,000)	25,191 (1:5,400)	35		13%	
					17%	9%

* The figures (1:42,000) denote one case of poliomyelitis to 42,000 persons. Figures are based on the approximate strength of the Army and the population of the United States. Data pertaining to Army personnel are preliminary and are obtained from two separate and not completely comparable sources. The cases shown for 1943-1946 and the deaths for 1944-1946 are derived from the periodic summary report, weekly statistical health report, and presumably include all cases of and deaths due to poliomyelitis, regardless of whether poliomyelitis was the cause of admission. These data may also erroneously include some cases on the basis of admitting diagnoses of poliomyelitis which were subsequently changed. Cases for 1940-1942 are based on tabulations of individual medical records where poliomyelitis was the cause of admission, while deaths for 1940-1943 are based on tabulations of individual medical records by cause of death. Use of these several sources makes the figures shown for per cent of mortality rather uncertain.

‡ From United States Public Health Service.

* Chief of communicable disease section, Letterman General Hospital, San Francisco, California.

† One female military dependent is included.

1. *Geographical Distribution:* The geographical occurrence of the cases is shown in Table 2.

2. *Age:* The recorded ages in 129 patients ranged from 17 years to 36 years, as shown in Table 3.

3. *Color:* Race is recorded in 147 patients. There were 139 whites and 8 negroes.

4. *Constitutional Factors:* The actual weights are not recorded in each case. However, the state of nutrition of military personnel may be assumed to be good. This is in accordance with findings of early writers on poliomyelitis, who state that the healthy, well-developed individual appears to be most susceptible to the disease.

TYPES OF CASES

In grouping of cases, the following classifications were used:

1. *Bulbar Spinal Type:* This group comprises patients with definite paralysis or paresis of muscles supplied by the spinal or cranial nerves.

2. *Bulbar Type:* This group includes patients with paralysis or weakness of the muscles supplied by the cranial nerves only.

3. *Encephalitic Type:* In this group are included cases characterized by cerebral involvement, usually indicated by high fever, prolonged stupor, disorientation, coma or convulsions.

One hundred and twenty-two were of the bulbar spinal type, 24 of the bulbar type, and three of the encephalitic type. There were 14 patients included among the bulbar spinal cases, who died of respiratory failure. These patients developed paralysis of the extremities, which ascended to produce dyspnea

TABLE 2.—*Area of Admission of 149 Selected Cases Terminating in Death, 1944-1945*

Location	No. of Cases	Per Cent
United States	51	34%
Philippines	42	28%
China, Burma, India	28	19%
European Theater	16	11%
Italy, Sicily	9	6%
North Africa	2	1%
Persian Gulf	1	1%

TABLE 3.—*Age Group Distribution in 129 Fatal Cases of Poliomyelitis*

Age	No. of Patients	Per Cent of Total
17-19	11	8
20-24	62	50
25-29	43	33
30-34	11	8
Over 35	2	1

and cyanosis. No notation of specific cranial nerve involvement appears in the clinical records of these patients, but all became comatose and died in the respirator, and it is felt that the infection should be classified as of the bulbar spinal type.

SYMPTOMS‡

It is generally stated that the symptoms of poliomyelitis are variable, and this is borne out by an analysis of this series.

Duration of Symptoms: Table 4 shows the duration of symptoms prior to hospitalization. Ninety-five per cent of the patients were hospitalized within five days of the onset of their symptoms. The proximity of medical officers to troops was no doubt responsible for early hospitalization.

TABLE 4.—*Duration of Symptoms in Days Prior to Admission to First Medical Installation in Series of 149 Fatal Cases of Poliomyelitis*

Duration	No. of Cases	Per Cent	Duration	No. of Cases	Per Cent
1 day	42	31	6 days	1	
2 days	39	27	7 days	2	
3 days	37	26	8 days	1	5
4 days	6	5	9 days	1	
5 days	8	6	10 days	1	

General Symptoms: In 137 patients, 92 per cent, the temperature was elevated at the time of hospitalization. The range of temperature varied considerably. There were 29 patients with temperatures above 104° F., including one in whom the temperature reached 110° F. In 12 patients there was no note of fever in the clinical records. It is very probable that fever was present, but not recorded.

Other general constitutional symptoms of frequent occurrence were headache, stiff neck, and weakness of the extremities as shown in Table 5. Hyperalgesia of the back, shoulders, pelvis and extremities were fairly common early in the disease. Skin rashes were described in two patients. In one the rash was morbilliform, generalized and appeared early in the disease and lasted about one day. In the other, the rash was urticarial and of short duration.

TABLE 5.—*Relative Frequency of General Symptoms*

Symptom	No. Having Symptom	Per Cent of Total
Fever	137	92
Headache	112	76
Stiff Neck	112	76
Weakness of extremities	96	64
Hyperalgesia	93	63
Backache	76	52
Tremor	25	17
Hypesthesia	17	11
Drowsiness	9	6
Convulsions	6	4
Lymphadenopathy	4	3
Rash	2	1

‡ Symptoms will be listed under the various systems for the purpose of classification. However, it is the opinion of other writers[3] on poliomyelitis that such manifestations as headache, vomiting, weakness, hyperalgesia, are all indicative of central nervous system disturbances and not of extraneural disease.

Gastro-intestinal Symptoms: Symptoms referable to the gastro-intestinal tract are shown in Table 6. Vomiting was the most common. Abdominal distention was often severe and required decompression measures and prostigmine for relief. One patient, who was eight months pregnant, was thought to have intestinal obstruction because of the severe abdominal distention and vomiting, and surgical intervention was considered. Two patients were admitted with a diagnosis of acute appendicitis.

TABLE 6.—*Gastro-Intestinal Symptoms*

Symptom	No. of Patients	Per Cent of Total
Vomiting	78	53
Abdominal distention	44	29
Abdominal pain	26	18
Constipation	16	10
Diarrhea	7	5

Respiratory Symptoms: The occurrence of respiratory symptoms is shown in Table 7. Dyspnea and cyanosis were frequent and were attributable to bulbar paralysis, involvement of the muscles of respiration or pulmonary involvement. Cyanosis accompanying the dyspnea was usually a terminal feature.

TABLE 7.—*Respiratory Symptoms*

Symptom	No. of Patients	Per Cent of Total
Dyspnea	128	86
Cyanosis	105	70
Nasopharyngitis	34	23
Sore Throat	23	16
Cough	14	10
Bronchitis	10	6

Genito-urinary Symptoms: Symptoms referable to the genito-urinary system are shown in Table 8. Urinary retention occurred in 73 patients (51 per cent), and persisted until death in 57 patients (38 per cent). There was spontaneous recovery of bladder control in 13 patients (9 per cent). Incontinence of urine developed in three patients (2 per cent). It has been stated by other writers[9] that retention of urine is a transient phenomenon and usually disappears during the course of the disease. In this series, in which all the cases were fatal, many of the patients died early in the illness. Hence it is difficult to appraise the duration of this manifestation. Most of those who regained bladder control did so during the first week. The longest interval of time required for recovery of bladder control was 21 days. In three patients, frequency and dysuria were the initial presenting symptoms and they were admitted with a diagnosis of prostatitis.

TABLE 8.—*Genito-Urinary Symptoms in 149 Fatal Cases of Poliomyelitis*

	No. of Cases	Per Cent
Inability to urinate	73	49
Persistent urinary retention	57	38
Recovery of bladder control	13	9
Incontinence of urine	3	2
Dysuria and frequency	3	2

Neurological Symptoms: The occurrence of neurological symptoms is shown in Table 9. The various manifestations often resembled those seen in the other diseases to which the symptoms were erroneously ascribed in early diagnosis, as will be noted later in Table 19. Stiff neck was more frequent than stiff back, which is contrary to textbook teachings.[8] Kernig's sign was noted in 40 patients, although it is very probable that it occurred more frequently, but was not recorded in the clinical records.

TABLE 9.—*Neurological Manifestations*

Sign	No. of Patients	Per Cent of Total
Nuchal rigidity	93	63
Disorientation	50	34
Muscle fibrillation	40	27
Kernig's sign	40	27
Stiff back	26	18
Head drop	16	11
Sensory changes	5	3

Paralysis: Distribution of Paralysis: The paralysis of muscle groups is shown in Table 10. One hundred twenty-two patients developed paresis or paralysis of the extremities. Paralysis of the intercostal muscles occurred in 69 per cent of the patients, and was more common than paralysis of the diaphragm (42 per cent), or abdominal muscle paralysis (14 per cent). Cranial nerve involvement is shown in Table 11. The tenth cranial nerve (vagus) was most commonly affected. Difficulty in swallowing was observed in 93 patients (63 per cent), as shown in Table 12. It appeared early and persisted until death in 73 patients (49 per cent). In 17 patients (13 per cent), it developed terminally. It was transient in only three patients. Difficulty in swallowing has been stated by other writers[2] to be a transitory phenomenon. Since death occurred in all these cases here reviewed, it is difficult to appraise the duration of this manifestation.

Interval Between Onset and Paralysis: This time interval was established in 122 patients. This relationship is shown in Table 13. It occurred within four days after the onset of the illness in 87 per cent of the patients, and during the first day of the disease in 14 per cent. Sudden paralysis in a previously healthy individual was observed. Several patients experienced paralysis in attempting to get out of bed to go to the latrine. One patient suddenly noted paralysis of his legs in getting out of a vehicle after a convoy trip over the Burma Road. Prodromal symptoms such as upper respiratory infections, malaise, or fatigue were present in many patients. It appeared that as long as an elevation of temperature persisted there was a possibility of the paralysis extending to uninvolved muscles.

Reflexes: Ninety-three patients (63 per cent) exhibited abnormal deep reflexes at the time of hospitalization or shortly thereafter. In 64 patients (42 per cent), absence of superficial reflexes (abdominals and cremasterics) developed during the course of the disease. The superficial reflexes invariably disappeared as the paralysis ascended to produce bulbar symptoms. Abnormal deep or superficial reflexes were not recorded in any of the patients with the pure bulbar type or encephalitic type of disease.

TABLE 10.—*Distribution of Muscular Paralysis in 149 Fatal Cases of Poliomyelitis*

	No. of Cases	Per Cent
Arms and legs	88	59
Arms only	19	13
Bilateral	13	....
Right	4	....
Left	2	....
Legs only	15	10
Bilateral	13	....
Left	2	....
Intercostal muscles	103	69
Diaphragm	63	42
Shoulder girdle	25	16
Abdominal muscles	22	14
Neck muscles	18	12

LABORATORY DATA

1. *Spinal Fluid:* The spinal fluid examinations were often incomplete, and data as to gross appearance, cell count, chemistry, serology, and colloidal gold were not available in all clinical records. The spinal fluid findings are shown in Tables 14 and 15.

TABLE 11.—*Cranial Nerve Paralysis in 149 Fatal Cases of Poliomyelitis*

		No. of Cases	Per Cent
II	Diminution of vision	5	3
III	Inequality of pupils	8	6
IV, VI	Ptosis of lids	7	5
VIII	Nystagmus	16	11
V	Weakness of jaw	3	2
IV, VI	Strabismus	8	5
	Diplopia	9	6
VII	Facial weakness	19	13
IX, X	Absent gag reflex	9	6
	Inability to clear throat	97	65
	Weakened voice	78	52
	Difficulty in swallowing	93	63
XI	Weakened neck muscles	18	12
XII	Tongue deviated	14	10

TABLE 12.—*Paralysis of Muscles of Deglutition in 149 Fatal Cases of Poliomyelitis*

Number of cases	93
Early onset and persisting until death	73
Developing with terminal phase	17
Transitory difficulty	3

TABLE 13.—*Interval Between Onset of Symptoms and Paralysis of Extremities*

	No. of Cases	Per Cent
1 day	17	14
2 days	45	37
3 days	32	26
4 days	12	10
Over 4 days	16	13
Total	122	
No paralysis of extremities	27	18

TABLE 14.—*Spinal Fluid Findings in 149 Fatal Cases of Poliomyelitis*

	No. of Cases	Per Cent
Gross appearance (124 cases)		
Clear	101	82
Opalescent	23	18
Cell Count (132 cases)		
Normal	18	14
10-50	24	18
50-100	16	12
100-500	59	45
500-1,000	10	8
Over 1,000	6	5
Lymphocytosis	55	56
Polymorphonucleosis	43	44
Protein (57 cases)		
Normal	9	15
40-80 mgm.	16	28
80-100 mgm.	14	25
Over 100 mgm.	18	32
Sugar (74 cases)		
Normal	41	55
70-100 mgm.	25	34
Over 100 mgm.	8	11
Chlorides (as NaCl) (21 cases)		
Normal	12	57
Elevated	8	38
Lowered	1	5
Colloidal gold curves (24 cases)		
Normal	9	39
Abnormal	15	61
Wassermann reaction (17 cases)		
Normal	16	94
Positive	1	6

TABLE 15.—*Spinal Fluid Findings in Bulbar Type Cases in 149 Fatal Cases of Poliomyelitis*

Spinal Fluid	No. of Cases	Per Cent
Cell Count (19 cases)		
Normal	6	32
10-50	3	15
50-100	3	15
100-500	6	32
500-1,000	1	4
Over 1,000	0	0
Cellular morphology (11 cases)		
Lymphocytosis	7	
Polymorphonucleosis	4	

Gross Appearance (124 patients): The spinal fluid was clear in 101 observations (82 per cent), and opalescent in 23 (18 per cent).

Cell Count (132 patients): Most laboratories accept the upper limits of normal as ten cells per cubic millimeter. The cell counts at the time of the initial spinal fluid examination, during the first week of the disease, were found to be elevated in 114 patients (86 per cent), and normal in 18 (14 per cent). Of the patients having normal cell counts, four showed an increase on subsequent examinations. The majority of the patients exhibited cell counts between 100 and 500 cells per cubic millimeter. The highest figure reported was 1,900 cells per cubic millimeter. Lymphocytes predominated in the majority of cases. It has been stated[7] that early in the disease the spinal fluid response is a preponderance of polymorphonuclear cells, and later there is a lymphocytic response. This was not observed in this series. Among the patients with the pure bulbar type of the disease, normal spinal fluid findings occurred in 32 per cent, and the cell counts when elevated were under 100 cells per cubic millimeter, with lymphocytes predominating in the majority of cases. No counts over 1,000 cells per cubic millimeter occurred in this latter group.

Quantitative Proteins (57 patients): Eighty-five per cent had spinal fluids with elevated protein content. Normal values were obtained in 15 per cent. There was no correlation between the protein content and the cell count.

Quantitative Sugar (74 patients): There were 33 patients (45 per cent), whose spinal fluid was found to have elevated sugar content, and of these, eight patients (11 per cent) had values above 100 mg. per cc. In no case was the spinal fluid sugar below normal. It has been reported that a highly elevated sugar content connotes a poor prognosis.[11] In this series, 87 per cent of the patients died within the first ten days of illness and the length of life could not be prognosticated from the spinal fluid sugar content.

Quantitative Chlorides: This was determined in only 21 patients. Normal values were found in 12 patients (57 per cent), and elevated values in eight patients (38 per cent). In only one instance was there reduction below the normal value.

Wassermann Reaction: The reaction to Wassermann test of the spinal fluid reported for 17 patients, was found to be negative in 16 and positive in one. There was no other evidence of syphilis in this one patient.

Colloidal Gold: Colloidal gold studies were reported in 24 patients, and the curves were abnormal, with no constant pattern, in 15 patients and normal in nine patients.

2. *Urine:* Urinalysis was performed in 98 instances and albuminuria ranging from 1+ to 4+ was encountered in 18 (21 per cent).

3. *Serology:* A Wassermann test of the blood was done in 17 cases and reactions in all were negative.

4. *Sedimentation Rate:* Blood sedimentation rates have been reported to be normal in poliomyelitis.[4] This determination was recorded in 23 cases shortly after hospitalization and was found to be normal in five (22 per cent), and elevated in 18 (78 per cent).

5. *Hematology:* Leukocyte counts were made in 124 cases at the time of hospitalization. Normal values (5,000 to 10,000) were noted in 41 (33 per cent). The majority of patients had leukocyte counts between 10,000 and 20,000. There were seven with counts above 20,000.

A summary of laboratory findings is shown in Table 16.

MORTALITY

The causes of death and the number of days by which death followed the onset of symptoms are shown in Tables 17 and 18. Autopsies were performed in 120 cases (80 per cent).

TABLE 16.—*Laboratory Findings in 149 Fatal Cases of Poliomyelitis*

	No. of Cases	Per Cent
Serology (17 cases)		
Normal	17	100
Sedimentation rate (23 cases)		
Normal	5	22
Elevated	18	78
Hematology (124 cases)		
Leukocyte count		
5,000-10,000	41	33
10,000-15,000	51	41
15,000-20,000	23	20
Over 20,000	7	6
Abnormal cells (Malaria)	2	
Urine (98 cases)		
Normal	80	79
Albuminuria	18	21

TABLE 17.—*Day of Death After Onset of Symptoms in 149 Fatal Cases of Poliomyelitis*

Day of Death (From Onset of Symptoms)					
1 day	3	10 days	4	22 days	1
2 days	4	11 days	3	23 days	1
3 days	24	12 days	2	41 days	1
4 days	18	13 days	2	56 days	1
5 days	20	14 days	1	58 days	1
6 days	14	15 days	1	85 days	1
7 days	18	16 days	1	130 days	1
8 days	18	17 days	1	135 days	1
9 days	5	19 days	1	170 days	1

TABLE 18.—*Principal Causes of Death in 149 Fatal Cases of Poliomyelitis*

Respiratory failure	99
Respiratory failure—Pneumonia	38
Pneumonia secondary cause of death	30
Pneumonia primary cause of death	8
Penicillin treated	27
No penicillin	11
Respiratory failure—Pulmonary edema	2
Respiratory failure—Pyelonephritis	1
Respiratory failure—Pneumonia, atelectasis	3
Respiratory failure—Pneumonia, myocarditis	2
Respiratory failure—Malaria	1
Severe toxemia	3

TABLE 19.—*Diagnosis Considered at Time of Admission and Subsequent Impressions Prior to Final Diagnosis in 149 Fatal Cases of Poliomyelitis*

Alcoholism	1	Psychoneurosis:	
Appendicitis	2	Battle fatigue	1
Arthralgia	1	Anuria	1
Arthritis	1	Hysteria	7
Bell's Palsy	1	Jitters	1
Dengue	13	Pyrexia, cause undetermined	21
Diphtheria	4	Pyelonephritis	1
Encephalitis	10	Retropharyngeal abscess	1
Gastro-enteritis	8	Salmonellosis	1
Guillain-Barre	9	Sandfly fever	3
Hepatitis	5	Sciatica	1
Hookworm	1	Sinusitis	3
Infectious mononucleosis	1	Spinal cord tumor	1
Influenza	5	Subacute bacterial endocarditis	1
Laryngotracheo-bronchitis	4	Subarachnoid hemorrhage	1
Malaria	12	Tetanus	1
Meningitis	36	Thrombophlebitis	1
Myasthenia gravis	1	Tick bite fever	1
Nasopharyngitis	18	Toxemia of pregnancy	1
Pelvic abscess	1	Typhoid fever	1
Periodic family paralysis	1	Undulant fever	1
Pneumonia	4	Vaccination reaction	1
Prostatitis	2		

CLINICAL PICTURE

From the data presented, it is obvious that there is nothing pathognomonic of the disease. No single symptom or sign was present in all cases. Temperature elevations were recorded in 92 per cent of the cases.

Spinal fluid cell counts were normal in 14 per cent. Spinal fluid protein determinations were normal in 15 per cent, and sugar values were normal in 55 per cent.

Symptoms of importance were headache, stiff neck, weakness of the extremities, hyperalgesia and backache. Among the gastro-intestinal symptoms of frequent occurrence were vomiting, abdominal pain and distention. Respiratory, genito-urinary, and nervous symptoms have been listed.

The diagnosis of poliomyelitis is difficult, as is shown in Table 19, which lists the impressions prior to the final diagnosis.

Thirty per cent of the cases were correctly diagnosed at the first medical installation at which the patient was observed. On physical examination, several findings were important. Stiff neck was frequent. Abnormal deep and superficial reflexes were present in the majority of cases. The disappearance of abdominal and cremasteric reflexes, which had been present earlier in the disease, were consistently associated with progressive bulbar involvement. Muscle paralysis appeared suddenly and was complete in some patients. In others, it was progressive over several days and in this group the fever was usually continuous. As long as fever continued, it was probable that the paralysis would spread. The accumulation of mucus in the throat, weakened voice and difficulty in swallowing directed attention to involvement of the tenth cranial nerve. The involvement of other cranial nerves has been listed.

In regard to the laboratory aids in the diagnosis, the spinal fluid examination, characterized by an increase in the cell count and protein content, provided important information. The average cell count was between 100 and 500 cells per cubic millimeter, but considerable variation occurred. In 85 per cent of the cases in which spinal fluid was tested for protein content the content was found to be elevated; in 32 per cent it was more than 100 mg. per cc. Hemograms revealed leukocyte counts between 10,000 and 20,000 in the majority of cases.

TREATMENT

Treatment instituted is included under the headings of (1) Special measures, (2) Symptomatic nonspecific measures and (3) Treatment based on errors in diagnosis. Since all cases were fatal, it is difficult to evaluate any method of therapy.

1. *Special Measures:*

Respirator: The respirator was used in 98 cases. The length of life in the machine and the sensorium at the time of its use is shown in Table 20. Eighty-one patients (82 per cent) died within the first three days. Three died while being transported to the respirator. It was used on 19 patients for whom no data as to the condition of the respiratory muscles appeared in the clinical record. The use of the respirator has been adequately covered.[14] It is common knowledge that the bulbar type is the most unfavorable form of the disease for the use of the respirator. The failure of the respirator, as evidenced by the high mortality within the first few days, is in accordance with the results of other observers.[4] There were some bulbar manifestations in all except the three cases of the encephalitic type of the disease. All patients surviving more than one week in the respirator were rational at the time they were put into it. The length of life of the patients who were rational at the time of use of the respirator, as compared with those who were irrational, is shown in Table 21. It would appear that the state of the sensorium at the time of use of the respirator was important.

Whole blood, plasma, albumin, antipoliomyelitis serum: These measures were used in 20 patients, the principle being to provide antibodies by using whole blood, plasma or anti-poliomyelitis serum, and to reduce edema of the nervous system by the use of albumin. The value of antibodies is questionable,[1] and no references are available regarding the use of albumin in poliomyelitis.

TABLE 20.—*Length of Life in Respirator in a Series of 149 Fatal Cases of Poliomyelitis*

	No. of Cases
Length of Life in Respirator	
Under one hour	7
1-12 hours	16
12-48 hours	48
3 days	10
4 days	1
5 days	2
6 days	2
8 days	1
9 days	1
13 days	1
16 days	2
40 days	1
56 days	2
73 days	1
125 days	1
135 days	1
170 days	1
Total	98
Died en route to respirator	3
Placed in respirator, but no note regarding respiratory muscles	19

TABLE 21.—*Sensorium at Time of Placing Patient in Respirator in a Series of 149 Fatal Cases of Poliomyelitis*

	No. of Cases
Rational	54
Irrational	44
Average length of life in respirator (Cases surviving under 8 days)	
Rational group	46 hours
Irrational group	19 hours

Kenny Principles: Twenty-three patients were treated by the application of heat to muscles exhibiting spasm. The evaluation of this method is difficult, since all cases were fatal. From notes in the clinical records, one gains the impression that the method was a failure. The literature contains numerous references to the Kenny principles,[6] and it will not be discussed in this paper.

Tracheotomy, intubation, bronchoscopic drainage, intratracheal suction: One patient was tracheotomized and another was intubated immediately following hospitalization because of respiratory distress, and death occurred within a few days after these operative procedures. In both patients the disease was erroneously diagnosed as acute laryngotracheobronchitis. Bronchoscopic aspiration was performed on two patients who developed atelectasis and pneumonia during protracted periods in the respirator and both died within 24 hours following the procedure. Intratracheal suction was performed on three patients, but all died within a few days of respiratory failure.

Spinal Drainage: Two patients were given hypertonic dextrose, and concomitant continuous spinal drainage was performed, without any degree of success.

Orthopedic Measures: The orthopedic aspects of the treatment will not be discussed in this paper.

2. *Non-Specific Therapeutic Measures:*

Oxygen: The administration of oxygen by mask, nasal catheter, or tent was used in 102 patients, the indications being severe toxemia, dyspnea, or cyanosis.

Penicillin: Penicillin was administered to 66 patients on an empirical or prophylactic basis with a view to combating secondary bacterial infection. Pneumonia was present on autopsy findings in 38 patients. Of these, 27 had been given penicillin. This would indicate that penicillin will not prevent pulmonary involvement in such cases. All patients exhibiting pneumonia at autopsy had been in the respirator. Bacterial studies to determine the type of the pneumonia were not available.

Sulfonamides: Sulfonamides by oral or intravenous routes were administered to 60 patients. The danger of sulfonamides in poliomyelitis has been stressed by Toomey.[10]

Other non-specific therapeutic measures included parenteral fluids, amigen, vitamins, stimulants, sedatives, analgesics, and drugs such as prostigmine, atropine, aminophylline, and streptomycin.

3. *Therapeutic Measures Based on Errors in Diagnosis:*

Penicillin Intrathecally: Penicillin intrathecally was administered to seven patients. The rationale

for this therapy was apparently based on a presumptive diagnosis of bacterial meningitis. One patient had a normal spinal fluid at the time of initial lumbar puncture, but was given 10,000 units of penicillin intrathecally. Within the next few hours the meningeal signs and symptoms increased and the temperature rose to 105° F. The following day the spinal fluid was found to be opalescent with 450 cells per cubic millimeter, all polymorphonuclears, and the patient died within 24 hours. Another patient died suddenly five hours after the administration of 10,000 units of penicillin intrathecally. The hazard of intrathecal penicillin has been reported by other observers.[5]

Other Erroneous Therapeutic Measures: One patient was given 300,000 units of tetanus anti-toxin by combined intrathecal and parenteral routes because of a diagnosis of possible tetanus. Another patient, with a diagnosis of hookworm infection because of the presence of hookworm ova in the stools, and paresthesias of the feet, was given tetrachlorethylene followed by saline purgations. His legs collapsed while he was making one of frequent trips to the latrine. Acute poliomyelitis finally was diagnosed and the patient died two days later. Another patient, who had been in combat on Luzon for 78 days, was examined in a collecting station because of weakness of the arms and legs. Upon a diagnosis of "battle fatigue" he was given a total dose of 2 gm. of sodium amytal intravenously. When the sedation effect disappeared, this patient's arms and legs were completely paralyzed. Respiratory difficulty required the use of the respirator and the patient died. One hundred thousand units of diphtheria anti-toxin was given to another patient who was thought to have laryngotracheobronchitis caused by diphtheria. There were seven cases in which a diagnosis of hysteria was based upon complaints of hyperalgesia and weakness of the arms and legs. These patients were treated on a sick-in-quarters status before paralysis developed and a final diagnosis of poliomyelitis was made. Another patient with generalized tremor of the arms and legs was returned to duty (after sedation) with a diagnosis of "jitters." Paralysis of both arms and legs developed and the patient died of respiratory paralysis three days later. Because of the incidence of dengue fever, malaria, and sandfly fever in the Pacific and Mediterranean areas, these diseases were frequently listed as the initial impression prior to a final diagnosis of poliomyelitis.

SUMMARY

Data taken from the clinical records of 149 fatal cases of poliomyelitis are analyzed.

The disease is less prevalent in the Army than among the general population, but the mortality among military personnel is higher.

The discussion of the classification of types of the disease and their incidence has been presented.

Symptoms:

a. Duration of symptoms: Ninety-six per cent of the patients were hospitalized within a few days of the onset of symptoms.

b. General symptoms: The temperature was recorded as elevated in 92 per cent of the patients at the time of hospitalization. Headache, stiff neck, and weakness of the extremities occurred in approximately 75 per cent of the cases. Hyperalgesia, involving the back, shoulders, pelvis or extremities occurred in 63 per cent of the cases. Backache occurred in over 50 per cent. Convulsions, lymphadenopathy and dysuria were rare. Skin rashes occurred in only two patients.

c. Gastro-intestinal symptoms: Vomiting, abdominal pain and distention were fairly common symptoms. Constipation was twice as frequent as diarrhea.

d. Repiratory symptoms: Dyspnea and cyanosis were frequently noted. Symptoms simulating an upper respiratory infection were present in approximately 25 per cent of the patients.

e. Genito-urinary symptoms: Urinary retention occurred in 51 per cent of the patients and persisted until death in 38 per cent. The phenomenon was transient in 9 per cent. Incontinence occurred in 3 per cent of the patients.

f. Nervous symptoms: Bulbar symptoms occurred in all except three patients with the encephalitic type of the disease. Of the cranial nerves involved, the tenth was the most frequently affected. Paralysis of deglutition was common and persisted until death in 49 per cent and was transient in only 2 per cent.

g. Paralysis of the extremities: Paralysis of the extremities occurred in 87 per cent of the patients within four days following the onset of symptoms and within one day in 14 per cent. An analysis of the distribution of muscle paralysis and reflex changes has been presented. The cremasteric and abdominal reflexes invariably disappeared as the paralysis ascended from the lower extremities to produce bulbar symptoms.

Laboratory Data:

a. Spinal fluid: The spinal fluid was usually clear. Normal cell counts were observed in 14 per cent of the cases. There was no absolute distinguishing characteristic in comparing the spinal fluid of patients with the pure bulbar type of the disease and that of the patients with the bulbar spinal type. The quantitative protein content was found to be elevated in 85 per cent of the spinal fluid examinations. An increase in the sugar was noted in 55 per cent. There was nothing characteristic in the cases in which the spinal fluid sugar content was high. Normal chloride values were found in 57 per cent. Colloidal gold curves were abnormal (but of no characteristic pattern) in 61 per cent. The Wassermann reaction was found to be positive in only one out of 17 cases in which the test was made.

b. Urine: Urinary findings were those observed in any febrile illness.

c. Serology: A Wassermann test of the blood was made in 17 cases and the reaction was negative in all.

d. Blood sedimentation rate: Sedimentation rate was determined in 23 cases and was found to be normal in 22 per cent and elevated in 78 per cent.

e. Hematology: The leukocyte response has been analyzed.

Mortality, clinical picture, diagnosis and therapeutic measures have been discussed. The short duration of life of patients treated in the respirator (82 per cent of the patients died within three days) has been noted.

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Dangers of Local External Heat and Trauma to Ischemic Tissues in Peripheral Vascular Diseases

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THE purpose of this article is to refresh the minds of the medical profession regarding the dangers of local heat or trauma to ischemic extremities. Every textbook discussing peripheral vascular diseases mentions the possibility of gangrene, burns or ulcer formation following the application of what normally would be considered safe and therapeutic amounts of heat. Regardless of the method of application, such as diathermy, infrared, electrical cradle, heating pad or hot water bottles, disastrous damage to the tissues might result. Extreme care is necessary.

Likewise, minimal trauma, such as bruising of the tissues or that caused by surgical removal of corns or calluses, or the application of caustic medications such as salicylic acid compounds, might be a source of danger in ischemic limbs.

As the author recently has observed an increasing number of such cases, it was felt that a brief review of the defective heat regulatory mechanism, as well as a discussion of the deficiency in healing of the ischemic tissues, might be timely. These cases are found most frequently in those suffering from arteriosclerosis obliterans, although thromboangiitis obliterans, generalized scleroderma, acute arterial occlusion and injuries to the arteries are frequently encountered. In addition, the decreased cellular activity of aging tissues as found principally in the more elderly arteriosclerotics, is a complicating factor in the healing process.

Ischemic tissues tolerate the local application of heat poorly. The basic principles are physiological and mechanical. These principles are:

1. Heat accumulates more quickly in ischemic tissues. The local heat regulatory mechanism cannot function properly. The normal physiological response to a rise in the environmental temperature of an extremity is an increased blood flow. On the application of external heat the vessels dilate, resulting in an increased flow of fresh blood which carries the heat away. Ordinarily this increased flow carries the locally heated blood to other parts of the body, chiefly to the surface, where the mechanism of radiation and increased perspiration cool it to normal. In the patient with arterial occlusion the increased blood flow is restricted. As a result the heat quickly accumulates in the tissues to dangerous levels.

2. External heat increases the metabolic activity of the cells. More oxygen is required and more waste products are formed. As a result, an increased blood flow is required. This increased demand cannot be met. The cells suffer acutely from the inability of the stenosed or occluded vessels to permit an increased blood flow required by a rise in local environmental temperature. Gangrene frequently supervenes.

3. Ischemic tissues lose their ability to discriminate between dangerous and safe degrees of heat. Nerve structures are very sensitive to a reduction in blood flow. Degenerative changes occur early. The receptor organs for warmth lose their efficiency. A much greater degree of heat is required to stimulate these end organs than would normally be necessary. It is possible for the individual to apply burning degrees of heat to an ischemic extremity without being aware of it.

The reaction of ischemic tissues to injury or infection is likewise affected. Frequently the arterial circulation is so poor that only minimal cellular activity can be maintained. Any additional burden such as that which is required in the healing process of injured or infected tissue cannot be met. This might even be impossible at absolute bed rest. The slightest skin abrasions will result in delayed healing or non-healing. Fungus infections of the toes in the presence of local ischemia are likewise potential sources of non-healing ulcers and gangrene. Caustic preparations for treating ringworm, those containing phenol, benzoic or salicylic acids, are also dangerous. Surgical removal of corns or calluses, or surgical treatment for ingrown toenails, occasionally is followed by serious results. It must also be kept in mind that the process of repair of tissue after injury is altered in the aged. Likewise the resistance of these aging cells to infection is inadequate. This throws an additional burden on an already ischemic tissue.

The following cases which were recently observed are illustrative of the problems involved. The patients were under constant medical care and had been repeatedly cautioned as to the effect of heat, caustics and trauma to the affected extremities.

CASE 1.—A 63-year-old man had arteriosclerosis obliterans with diabetes mellitus of many years' duration. The diabetes was well controlled. The blood sugar levels were usually about 100 mg. per 100 cc. The patient had suffered from severe intermittent claudication for the preceding three years. Acute occlusion of the right femoral artery, apparently on an atheromatous basis, had developed about a year previously. This was followed by an ulcer of the dorsum of the foot which required several months to heal. The ischemic symptoms partially subsided. The patient, who was ambulatory, visited a chiropodist who trimmed his toenails, and signs of early infection in a small abrasion alongside the nail of the right big toe followed. In spite of intensive therapy with large doses of penicillin, Tyrothricin solution locally, x-ray therapy locally and absolute bed rest, the infection spread, resulting in a painful ulcer of the distal portion of the toe. The big toe soon became completely gangrenous. Two months after the initial trauma, amputation of the leg below the knee was necessary. The wound healed by primary intention.

CASE 2.—The patient, a 60-year-old woman with severe generalized scleroderma, had been under constant observation for over a year, then was lost sight of for five months. On her return she was found to have dry gangrene of the fourth and fifth toes of one foot, with intense pain. She said that she had been under medical care in the interim and that, as her feet were frequently cold, another physician had advised the use of local heat. She then applied an electric pad at low heat. After two or three nights the toes became dark and discolored. The two toes quickly became gangrenous. Within three weeks the distal half of the foot was involved in the gangrenous process. The patient died before surgical operation could be attempted.

CASE 3.—The patient, a woman 64 years of age, had arteriosclerosis obliterans with diabetes mellitus. The diabetes, which was of long standing, was well controlled by diet. Moderate intermittent claudication had been complained of for about two years. There was an acute occlusion of the left femoral artery. The ischemic symptoms subsided in about two months. In getting out of bed, the patient struck the affected foot against the metal side, causing a slight abrasion of the dorsum of the middle toe. This showed no indication of healing, although the rest of the foot was in good condition. After three weeks the area of abrasion suddenly started to show signs of discoloration. The entire toe rapidly became gangrenous, to be followed within a week by the adjoining toes. Within three weeks of the flare-up the distal third of the foot was involved and a mid-thigh amputation became necessary.

In reviewing these cases one cannot definitely state that the gangrenous processes were touched off by traumata. However, as progress had been satisfactory in each case until the time of trauma, by heat, impact or caustic medication, it is felt that the gangrene would not have developed spontaneously.

CONCLUSION

Attention is called to the potential dangers of external heat, impact, trauma, infection or caustic medication to ischemic tissues found in peripheral vascular diseases.

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Correction

An error was made in a footnote to the article, "The Berman Foreign Body Locator," by J. P. McBride, M.D., which appeared on page 276 of the October issue of CALIFORNIA MEDICINE. The footnote appeared: "The biplane fluoroscope developed by Leishman may also prove to be an additional aid in exact location at the time of operation." It should have been worded: "The stereoscopic fluoroscope developed by Leishman may also prove to be an additional aid in exact location at the time of operation."

CASE REPORTS

◀ Hereditary Angioneurotic Edema: A Remarkable Family History ◀ Charcot's Joint With Secondary Purulent Arthritis Treated With Intra-arterial Penicillin

Hereditary Angioneurotic Edema: A Remarkable Family History

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"I SHALL never forget a case in which my healing art would have proved unavailing and which would have terminated fatally had it not been for the advice of a worthy colleague. The disease was quite new to me in its manifestations and was amazing because of its sudden relapses. I will tell you briefly the whole story because it is to me the strangest of all my medical tales.

"A worthy gentleman, who, as a result of his sober way of living, had attained his 62nd year, awoke one morning with a remarkably puffy face. The lips and eyelids were unbelievably swollen, looking much as if he had been stung by a bee or a wasp. The swelling was lymphatic, without noticeable inflammation, and entirely without pain, burning, or itching. The pulse was natural and the body entirely healthy, though I should not forget to mention that he had suffered every winter from a kind of rheumatic cough from which he always recovered without medical aid.

"But this winter, instead of the usual cough, this strange malady appeared. I ordered the patient to bed and gave him draughts of elderberry tea with liquor anodinus and left the rest to nature. The swelling had completely disappeared by afternoon; it had left the face and descended to the scrotum. The patient felt the arrival there of the new swelling as a brief, sharp sting. Inside of fifteen minutes the whole scrotum was swollen larger than an ox bladder, like a monstrous hydrocele. But there was no burning, pain, or itching; nor were there chills, fever, or thirst. I saw no danger and deemed it a passing acrimony of the humors not yet ripened and ready for transpiration, so I stood fast by the elderberry tea which I had previously ordered and hoped for a healing sweat. I laid cotton soaked in juniper and burnt sugar on the edematous scrotum, and inside of five or six hours the malevolent trouble disappeared and flew to the tongue.

"The tongue could no longer find room in the throat. It swelled out through the lips and filled all who saw it with pity and fear. Now it was time to put other strings to our bow, to employ mightier means against this dangerous fellow. There was good reason to fear that the malicious vagabond might take a notion to invade the windpipe, the lungs, or the brain and cause deadly damage there. Cupping was tried, then blisters, sweats and emulsions of camphor; but the swelling remained stubborn, changing its place every day. Now it was the left, now the right ear, now both; now the eyelids, or the forehead, now the arm. A consultant suggested that the cause of the frequent relapses might be found in the digestive tract. Fortunately, this proved to be the case as the repeated use of tartar emetic alone was able to ban this remarkable and dangerous evil, which, with the continued use of the impotent elderberry tea, might perhaps have killed the patient in spite of his sound heart."

Franz Anton Mai, Professor at Heidelberg, published in 1777 a charming, widely-read book entitled, "Stolpertus, a Young Doctor at the Bedside," which contains this report of a case of angioneurotic edema.[16] The frontispiece woodcuts from the same work show the close association of the doctor of that time with the graveyard, a rare insight in a medical contemporary.

Mannheim
Bei C. F. Schwan, kuhrfürstl. Hofbuchhändler.
1777.

Mannheim,
bei C. F. Schwan, kurfürstl. Hofbuchhändler.
1778.

The disease may be defined as a transient edema which may involve the skin, mucous membranes, subcutaneous tissue and muscle; usually migratory, one swelling subsiding as another develops. It was well described by Quincke[20] in 1882 under the name of acute circumscribed edema and is often referred to as Quincke's disease or Quincke's edema. Among the other names for it in the early literature are "ephemeral congestive tumors of the skin," "ephemeral cutaneous nodosities," "giant hives," "wandering edema." Recognizing the neurotic element, Strübing[1] first called it "angioneurotic edema" in 1885. Osler,[18] in 1888, published an excellent description of the familial type. The typical swelling may involve a hand, or forearm and hand, or the face or some part of it, the lips and tongue, or the external genitalia, in fact, any part of the body surface. The swelling is usually of a brawny hardness, the border often being sharply demarcated from the adjacent normal tissue. Involvement of the hand makes flexion of the fingers impossible and the member useless. The swellings are deep and may involve skin, subcutaneous tissue and muscle; the skin is glossy and taut and subcutaneous bullae may be present. There is no inflammation.

In addition to the surface swelling, internal organs and tissues may be involved. Swelling of the mucous membranes and of the subjacent tissues is common, particularly in the region of the mouth and larynx. Swellings of the lips and tongue make speaking and eating difficult. Involvement of the larynx may cause partial obstruction with stridor, cyanosis and labored breathing, or complete obstruction with death from asphyxiation. The edema may extend to the bronchial mucosa. However, there is some doubt about the classification of certain cases of transient localized areas of edema of the lungs with roentgenographic findings similar to those of tuberculosis. They are described as visceral manifestations of angioneurotic edema, but should probably be classed as examples of Löffler's syndrome, or as a manifestation of a disseminated visceral angiitis.

Severe cramp-like abdominal pain is a common symptom either accompanying surface swelling, or occurring in persons subject to the disease. The pain may be substernal or epigastric, suggesting swelling of the esophagus or stomach, or there may be generalized or localized abdominal pain, often accompanied by nausea and vomiting, or diarrhea, or both. The vomitus or stools may be grossly bloody and death has occurred in severe attacks.[17] Because the findings resemble so closely those of appendicitis,[22] biliary colic, or perforated peptic ulcer, with localized tenderness, muscle spasm, fever and leukocytosis, operations have been performed during an attack with various interesting findings.

A tense, swollen cecum and first portion of the ascending colon, with considerable retroperitoneal edema, was reported in one case.[22] No abnormality at all may be discovered except for large amounts of free peritoneal fluid.[8] Lundbaek[15] examined a patient gastroscopically during an attack of abdominal pain and found the entire mucous membrane of the stomach succulent in appearance. The folds were broad as if distended, the color deeper red than normal. There were no erosions and no exudate. Reexamination after the attack had subsided showed a normal mucosa. Attacks resembling ureteral colic with hematuria have occurred in this disease. Oliguria may be noted with attacks involving any portion of the body followed by polyuria as the attack subsides. One case of oliguria with angioneurotic edema occurring during pregnancy has been described, with relief obtained by giving theobromine and aminophyllin.[26] The baby born of this mother developed the typical swellings of the disease 56 hours postpartum. Swelling of the uterus and Fallopian tubes may occur.[4] Hydrarthrosis may be a manifestation of the disease.[21]

The nervous system is not immune to attack. A patient with signs of a brain tumor, including choked discs, vomiting and headache, was found at operation to have only edematous brain tissue.[1] He subsequently developed a typical attack of angioneurotic edema and the neurological signs cleared completely. An attack of transient hemiplegia with aphasia is described and certain migraines are believed to be angioneurotic.[1] A remarkable case of relapsing proptosis due to retrobulbar swelling has been reported. Recurring swellings of the eyelids accompanied by iritis with increased ocular tension and great pain occurred in a patient who also had attacks of Menière's disease.[13]

The disease is of two main types, the familial and the sporadic. Unfortunately, this distinction frequently is not made in the literature and some confusion results. The sporadic type, which may be acute or recurrent, is undoubtedly an allergic disease and occurs in persons and families with other allergic manifestations. There is no history in this form of the disease, however, of its occurrence in members of the family through generation after generation. It is common for an isolated attack to occur, or for the attacks to be limited to a period of weeks or months. Rarely they may extend over two or three years. In the familial disease, attacks recur irregularly throughout life. In sporadic cases, hives, a scarletiniform rash, or erythema multiforme may accompany the angioneurotic edema, and pruritus is often very distressing.

In differential diagnosis the following list of diseases with somewhat similar symptoms must be considered: Henoch's or Schönlein's purpura, Osler's erythema group of skin diseases with visceral manifestations, disseminated lupus erythematosus, periarteritis nodosa, Löffler's syndrome, Libman-Sachs disease, and possibly nephrosis.

Pruritus, skin rashes, purpura, arthritis and the other systemic diseases just mentioned are not a part of the familial type of angioneurotic edema. Except for the hazard of death from edema of the glottis, it is a benign disease compatible with long life and good health. Attacks of abdominal pain with nausea and vomiting occur in both forms. A very striking difference between the two is that edema of the glottis is a common cause of death in the familial type, but probably does not occur in the sporadic form, although there may be discomfort and apprehension from swelling in that region. The importance of allergy in the sporadic form is indicated by the many reports of cures by desensitization or by elimination of the allergen. The allergens reported are numerous and curious. Foods and inhalants are common. Rowe[23] reports cures with careful elimination diets. Dorst[5] was successful in certain cases in desensitization with vaccines made from bacteria grown from the intestinal tract as well as from infected nasal sinuses and gallbladders. Drugs are common offenders, the coal tar drugs particularly.[3] Estrogenic substances,[24] chlorine in chlorinated drinking water,[14] and chicle[11] in chewing gum are reported as causes of angioneurotic edema. The disease has followed the use of diphtheria antitoxin and also quinine in the treatment of malaria. There are various precipitating factors in the individual attacks; mild physical trauma, like a bump on the head, may be followed by a swelling starting in the region of the trauma; a tight shoe, a fold in the clothing under the buttocks, are cited as precipitating causes. Exposure to cold or wind may precede attacks. Psychic causes are common; unusual emotion—pleasant or otherwise—undue nervous or physical fatigue, may be factors.

The hereditary factor in the familial type is very striking. Osler[18] in 1888 reported a family of 36 members with the disease occurring in several generations. In 1929 Dunlap and Lemon[7] tabulated 21 families from the literature and added one of their own. In the family here reported the disease extends through four generations. There are eight members, a grandfather, a son and daughter, one grandson

and three granddaughters, all of whom were affected. Two died of edema of the glottis.

Susceptibility to the disease is apparently a Mendelian dominant character without sex linkage (male and female are both affected) and there is usually no skipping of generations. Although the appearance and behavior of the swellings are so strikingly similar to those in the allergenic disease, there is great doubt that allergy is causative in the familial form. Certainly, search for allergens, elimination diets and immunization with vaccines have been futile in the familial type of the disease. Theories regarding the cause or causes of this disease and the pathological physiology of the swellings may be mentioned. Strübing, noting the fact that the disease occurred in high-strung, nervous individuals, thought that there was a disturbance of the nervous control of capillaries with a dilatation and exudation of fluid into the tissues.

Hives can be produced experimentally by injecting eserine, a cholinergic drug. However, direct stimulation of cholinergic nerves will not cause hives, refuting the theory that the psychosomatic influence alone causes anigoneurotic edema. Eserine applied locally causes the cells to liberate "H" substance, which initiates a wheal.[3]

Rowe[23] believes that all cases are allergic in nature. Other investigators, including Drysdale and Piness and Miller,[6] think that the hard, pale, non-itching swelling of the familial type is not due to allergy. Farquharson[9] believes both types have constitutional factors, by virtue of which an urticarial reaction is more easily elicited. He notes that both types occur in nervous, sensitive individuals and both are made worse by the patient's worrying about the condition. Farquharson relies on psychotherapy and stresses the fact that the allergen often cannot be found even in the sporadic cases.

Various blood studies have been carried out on patients during attacks. In some cases, counts of erythrocytes and leukocytes and hemoglobin and differentials may be found to be within normal limits. On the other hand, with abdominal pain especially, a high leukocytosis may occur with or without eosinophilia.[12] One wonders whether the attacks of abdominal pain with eosinophilia should not more properly be classified with the group of diseases included in visceral angiitis. The serum albumin-globulin ratio is said to be increased.[7] Black[2] treated patients with vitamin K on the theory that prothrombin formation might have something to do with the permeability of the capillary wall and that this mechanism might be affected by the administration of vitamin K. He found a good percentage of patients with prolonged prothrombin time and obtained relief of symptoms in many cases. Some patients with normal prothrombin time were also benefited.

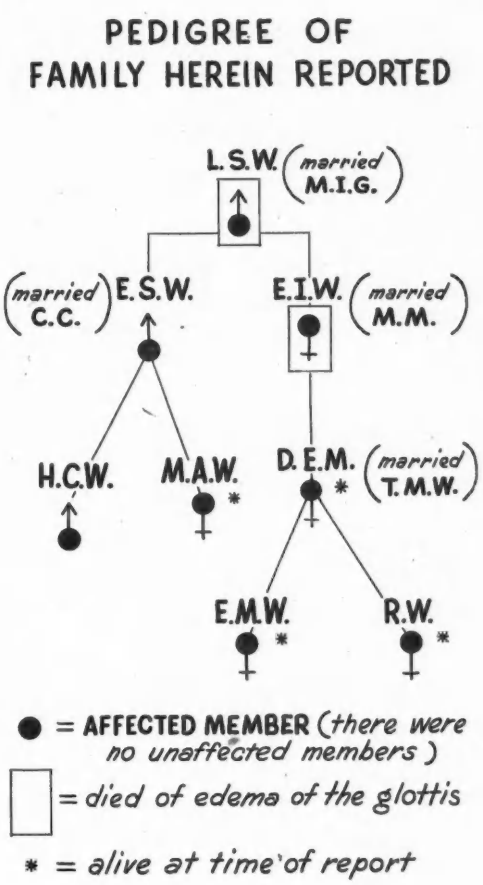
Endocrine dysfunction has been considered a cause of angioneurotic edema. Certainly in the family here reported there are no stigmata of such disorders, and medication with thyroid, parathyroid and ovarian extracts has been of no value.

CASE REPORT

The family here reported is remarkable in that every member was affected. L. S. W. was the first one known to have had the disease, although his mother was thought to have had it. He had two children, E. S. W. and E. I. W., both of whom were affected. L. S. W. died in his twenties from a swelling following a tooth extraction. His son, E. S. W., suffered swellings only occasionally and they became less frequent as he grew older. E. S. W.'s niece remembers one swelling of her uncle's hand caused by the pressure of his thumb over the nozzle of a hose. He died at 47 from another cause. E. S. W. had two children, H. C. W. and M. A. W., both of whom were afflicted. The boy was known to have had one swelling which was thought to have started from the pressure of his watch on his cheek when it slipped down from under his pillow at night. As far as is known, he did not have serious trouble with the swellings. His sister is still alive, quite an old lady, thin and delicate in health. She remembers her first attack—in the throat at the age of 17. She had frequent attacks in her hands and feet during her girlhood. Later, she had only one or two attacks for a period of 13 years, although still later she suffered again from very frequent swellings. She feels that food causes swellings and is also convinced that the swellings are more apt to occur when she is weak and nervous. E. I. W., the daughter of L. S. W., suffered the usual swellings of the extremities and

TABLE 1.—*Tabulation of Cases of Angioneurotic Edema of the Familial Type Collected from the Literature by Dunlap and Lemon in 1929*

	Generations	Members	Members Affected	Deaths	
Osler	6	42	24	2	
Crowder and Crowder	5	64	28	15	
Ricochon	4	....	9	3	
Schlesinger[25]	4	15	5	....	
Ensor	5	80	33	12	
Dinkelacher	2	4	3	....	3rd member reported by Valentin
Strübing	2	4	3	....	Father, son, daughter
Falcone	3	....	2	....	Grandfather and child
Krieger	2	....	2	....	Mother and son
Fritz	3	9	8	5	Deaths from edema of glottis
Roy	2	....	2	....	Mother and daughter
Yarian	2	15	10	2	One death from edema of glottis
Griffith	2	....	2	2	Father and patient died from edema of glottis
Harbitz	3	....	6	....	
Morris	2	....	3	1	Death from edema of glottis
Halsted	3	....	7	....	
Halsted	2	....	4	....	
Halsted	2	....	3	....	
Smith	2	....	2	....	Mother and daughter
Mendel	4	12	9	6	Deaths from edema of the glottis
d'Appert and Delile	3	....	5	....	
Dunlap and Lemon	4	23	11	6	Two died of edema of glottis



had seven or eight attacks in her throat. Once it was thought to have been caused by leaning her forehead against her hymn book in church. The inhalation of steam from boiling vinegar was believed to bring relief. She died at the age of 27, when her daughter, D. M. W., was three months old. She was standing by the stove and fell dead. Autopsy showed death from asphyxiation due to swelling of the larynx.

D. M. W., living in 1947, aged 73, was the source of information regarding her family. Her first attack, she was told, was when she was 3 or 4. She suffered attacks of acute abdominal pain during childhood which were called bilious attacks. The first swelling she remembers occurred when she was 17. It was in her hand or arm and came during a period of illness in the family, when she was anxious and depressed. She had attacks of stomach trouble at this time and frequent swellings of hands and face. She was treated with stomach lavage and iron. Her first prolonged period of migratory swellings occurred during her first pregnancy and lasted ten days. She suffered many swellings in her throat, some of them producing difficulty of breathing and cyanosis. On two occasions, obstruction to breathing was complete and tracheotomy became necessary.

This woman, as can readily be imagined, was constantly haunted by fear of her disease. She suffered from malnutrition at one time, due entirely to a fear of causing a swelling by some food. She was almost entirely free of attacks during the two years her husband was away from home during the first World War, and had a comparatively long period of freedom following a severe attack of measles in adult life. The attacks, except when they involved the digestive tract and throat, were not painful but were usually accompanied by malaise of sufficient degree to cause her to take to her bed.

Her daughters, E. M. W., aged 43, and R. W., aged 42, have the disease in forms similar to their mother's except that they suffer less malaise. Both have had attacks of severe abdominal pain, however, requiring morphine for relief. E. M. W. was operated upon for appendicitis during one attack which resembled that disease closely. There were a leukocytosis of 22,000 with 90 per cent polymorphonuclears, exquisite tenderness at McBurney's point and rebound tenderness. At operation, a normal appendix was found but the peritoneal cavity was full of a pinkish fluid which coagulated instantly on cooling. The patient recovered uneventfully and was absolutely free from swellings for two years after the operation.

R. W.'s story is in most respects similar to her sister's—swellings of extremities and face, and abdominal colic. She had one attack of edema of the glottis necessitating tracheotomy. These sisters, the last of the line, are unmarried.

Attempts at therapy have been numerous and futile. D. E. W. was skin tested, and although she gave positive reactions to certain foods, dust and pollens, elimination diets and immunization to other allergens were of no benefit. Vaccines made from her intestinal flora were tried. The following were used unsuccessfully in treatment of this patient:

Adrenalin	Ephedrine
Pituitrin	Thyroid
Bromides	Vitamin B 1 and B 6
Chloral	Ultraviolet rays
Atropine	Soda
Pilocarpine	Autogenous vaccine from intestinal flora
Histamine	
Benadryl	Parathormone
Ovarian extract	Gynergen
Aspirin	Activin
Morphine	Torantil
Calcium lactate	Pyribenzamine

Those that were suggested but not tried were insulin, bee venom, autogenous blood, horse serum, Vitamin K, and x-ray.

300 Homer Avenue.

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Charcot's Joint With Secondary Purulent Arthritis Treated With Intra-arterial Penicillin

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SECONDARILY infected tertiary syphilitic lesions are frequently equally resistant to anti-syphilitic measures with either the heavy metals or antibiotics and present a difficult therapeutic problem. A standard treatment by arsenicals or bismuth is ineffectual because of the superimposed bacterial infection, and although penicillin may be effective against the particular infecting bacteria and also treponemacidal, it may fail when administered intramuscularly or intravenously because of the poor permeation into the involved region. Local factors of impaired vascularity and fibro-osseous barriers prevent penicillin from gaining entrance into the involved area when the drug is administered by the intramuscular or intravenous methods; but, fortunately, by the intra-arterial route it is possible to overcome these barriers and thus achieve the desired therapeutic result. The following case report illustrates that after the failure of intramuscular penicillin therapy of a secondarily infected syphilitic lesion a prompt desirable result attended treatment with smaller dosages of penicillin given by the intra-arterial route.

From the Surgical Service of Owen H. Wangensteen, M.D., University of Minnesota Hospital.

CASE REPORT

The patient, a man 64 years of age, had had swelling and purulent drainage from his left foot over a ten-year period (1935-1945) and had been incapacitated because of it many times. Since May, 1945, there had been an exacerbation of symptoms and he was finally admitted to a hospital in mid-August, 1945, and given a six-day course of 20,000 units of penicillin intramuscularly every three hours (160,000 units daily). This had no effect on the swelling or purulent drainage and both conditions continued to increase in severity. On referral of the patient to the University of Minnesota Hospital on 27 September, 1945, physical examination revealed a small, thin, fairly well developed man with a temperature of 102° F. and a pulse rate of 100 per minute. There were erythema and edema of the medial distal one-half of the left foot and two indurated purulent draining sinuses on the plantar surface of the first metatarsal of the foot. A moderate edema of the left leg extended up to the knee and an enlarged tender left inguinal node was palpated in the groin. The blood pressure was 165 mm. of mercury systolic and 68 mm. diastolic, but the heart was otherwise normal, as were the lungs.

Neurological examination of the patient revealed that the pupils reacted sluggishly to light but normally to accommodation. Anisocoria was present, with the right pupil larger than the left. Knee jerks and ankle jerks were diminished and posterior spinal column disease was further evidenced by a positive Rhomberg test, decreased muscle, tendon, joint, and testicular pain, and decreased sense of vibration and position in the lower extremities. Superficial sensation was intact. As to mental status the patient was of normal intelligence with no gross abnormalities. Venereal history was denied but a clinical diagnosis of tabes dorsalis with Charcot's joint of the foot was confirmed by a neuropsychiatric consultant. Laboratory studies revealed a hemoglobin of 10.4 gm. and a leukocyte count of 13,850 per cubic millimeter with a differential count of 84% neutrophiles and 16% lymphocytes. The blood sedimentation rate was 120 mm. in 60 minutes (Westergen). Blood chemistry determinations, including fasting blood sugar, were within normal limits. Upon urinalysis a trace of albumin and an occasional cast were found. A culture of the purulent exudate from the foot revealed coagulase-positive staphylococcus aureus to be present. Results of initial serological tests for syphilis were: Kline, doubtful; Hinton, doubtful; Kahn, negative. Subsequently, reactions to the Kolmer test were negative, to the Kline test 2+, and to the Eagle test 3+. The spinal fluid cell count was normal (2 cells per cubic millimeter) but the protein was elevated to 304 milligrams per 100 cc. A first zone colloidal gold curve was present but results of spinal serology were negative. A roentgenogram of the foot (Figure 1) showed a destruction of the first metatarsophalangeal joint with considerable fragmentation and new bone formation in the soft tissues characteristic of Charcot's joint with probable secondary purulent arthritis present.

Intra-arterial injections of 50,000 units of penicillin were given into the femoral artery twice daily over a five-day period until a total of nine injections had been given. The penicillin was diluted in 10 cc. of normal saline and given into the femoral artery in a perpendicular plane using a 10 cc. syringe and a 20-gauge two and one-half inch needle. A blood pressure cuff was placed on the left thigh and inflated to 80 mm. of mercury prior to the intra-arterial injection and maintained at that pressure for ten minutes following each injection. Foot soaks of potassium permanganate solution (1:9000 concentration) were used twice daily as a therapeutic adjunct. The cellulitis cleared entirely in 48 hours and drainage ceased in 72 hours. Following intra-arterial penicillin therapy a sterile dressing was applied to the foot and the skin had entirely grown over the sinus tracts

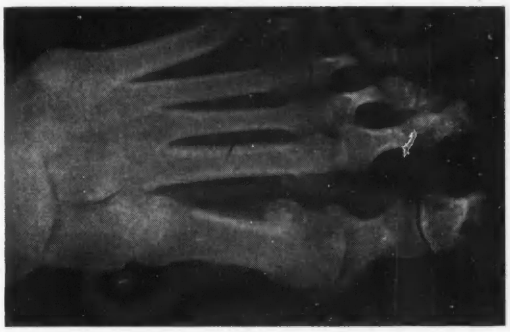

Figure 1.—X-ray of left foot revealing destruction of the first metatarso-phalangeal joint and new bone formation in the soft tissues characteristic of a Charcot's joint.

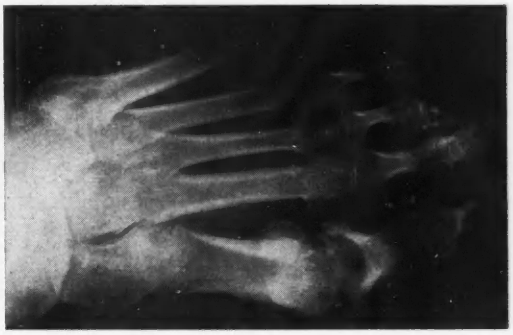

Figure 2.—X-ray revealing increase in density at first metatarso-phalangeal joint and no evidence of residual infection five months after hospital discharge.

within two weeks of the start of therapy. The patient was able to walk on the foot without difficulty following this and was discharged from the hospital on 24 October, 1945. A roentgenogram of the foot (Figure 2) taken 6 March, 1946, showed an increase in the density in the bone in the involved area at the first metatarso-phalangeal joint. There was no evidence of residual infection in the foot. The patient was followed by the neuropsychiatric clinic concerning the tabes dorsalis but had had no further difficulty with the left foot when seen one year after hospital discharge.

COMMENT

In a generalized infection without abscesses (septicemia) the determining factor of successful penicillin treatment is the effective bacteriostatic level of penicillin required in the serum as determined by the penicillin sensitivity of the infecting organism, but in a local area of suppuration (abscess) in an extremity, the permeability of the wall of the cavity is the more important since fortunately most of the bacteria found in infections of the extremities are sensitive to penicillin.[2]

Thus, in septicemia, penicillin may be given in the required dosage by the usual intramuscular or intravenous routes depending upon the sensitivity of the organism. However, in abscesses even a high concentration of penicillin in the serum may be ineffectual and the method of administration must be altered so as to obtain an effective penicillin concentration locally within the abscess. In many infections of the extremities the large area involved and the presence of multiple fascial and bony pockets have made local injection untenable but fortunately intra-arterial penicillin has been found to be efficacious in these cases. In addition the use of a blood pressure cuff placed just about the knee and inflated to a subdiastolic pressure (80 mm. mercury) prior to the intra-arterial injection and for the 10 minutes following, obstructs the venous return but permits the systolic pressure to force the concentrated drug into the local area supplied by the artery without significantly increasing the dilution of the drug.

The comparative efficacy of the intravenous and intra-arterial methods was borne out by an experimental study using radioactive phosphorus (P_{32}) and a Geiger counter for tracing in a series of normal subjects.[1] These studies revealed that every determination in the toes, dorsum of the feet, and midcalf of normal subjects, who were given radioactive phosphorus intra-arterially with a proximally placed blood pressure cuff inflated to 80 millimeters of mercury for stasis, was over the intravenous mean value for a period of three hours. This indicates that this intra-arterial method gives a higher concentration in the leg than the intravenous method during this time. For the first hour the mean Geiger counts of the determinations done on the toes and dorsum of the feet were over twice the values later determined by intravenous injection in the same subjects. Maximal values obtained with intra-arterial injection and a blood pressure cuff for stasis remained over twice the maximal values obtained by intra-arterial injection without a cuff for a period of 30 minutes and did not fall to the level of maximum values without a stasis cuff for one and one-half hours, indicating the stasis cuff permits a higher concentration than the simple intra-arterial injection for one and one-half hours. With the stasis cuff at 280 millimeters of mercury minimum values were occasionally below the mean for the intravenous method for the initial 30 minutes, indicating that the radioactive phosphorus may be withheld during this time and suggesting that the stasis cuff at 80 millimeters of mercury gives more consistent results.

Since the method of administration of penicillin is a more important variable than the dosage of penicillin, the therapeutic result in the case herein reported was better from a small dosage of penicillin given intra-arterially than was obtained from a larger dosage of penicillin given intramuscularly. The simple technique of intra-arterial injection has previously been described elsewhere and its safety is exemplified by a previously reported case of a 70-year-old woman who received a total of 30 intra-arterial injections at approximately the same site in the common femoral artery over a period of 16 days without hematoma formation or any other difficulty.[2] The present case is presented as an example of the efficacy of penicillin given intra-arterially.

SUMMARY

1. A report of a case is presented in which a patient with a secondarily infected Charcot's joint of the foot was not benefited by penicillin given intramuscularly but experienced good results later when a smaller amount of the drug was given intra-arterially.

2. Intra-arterial injection of penicillin is suggested for the treatment of secondarily infected syphilitic lesions of the extremities.

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CLINICAL SYMPOSIUM

Prepared under the direction of EDGAR WAYBURN, M.D., *San Francisco*, and CLARENCE J. BERNE, M.D., *Los Angeles*

The Management of Peripheral Vascular Insufficiency In Arteriosclerosis Obliterans

PATHOLOGY: DR. BENJAMIN E. KONWALER*

The arterial changes which occur from infancy to old age, without apparent disease, are well known. These comprise thickening and reduplication of the internal elastic membrane, calcification of the media, and may include fatty infiltration and hyaline degeneration. It is not entirely obvious which of these changes are physiologic and which are pathologic. However, the evidence is strong that arteriosclerosis may be, in part, not only pathologic but even reversible. Thus lipemia, hypertension, and diabetes mellitus may accelerate the progress of arteriosclerosis, while wasting disease may effect a reversal of the process.

Arteriosclerosis obliterans of the peripheral arteries is clinically considered to be part of a generalized condition associated with old age. However, the histological foundation for its development may appear as early as the first decade of life.

In the non-diabetic person, the arterial change seen in the muscular vessels of the extremities is predominantly the Monckeberg type of sclerosis with medial calcification. This lesion is distinct from the atheromatous process which may be encountered in elastic vessels, such as the aorta. There is little, if any, relationship between the medial type of arteriosclerosis and the atheromatous. Furthermore, the degree of involvement of different muscular arteries in any one patient is far from uniform, so that there is no necessary association of advanced arteriosclerosis of the extremities with a comparable process in the arteries of the heart, of the kidneys or of other regions.

If the pathologic changes remain limited to the media, the lumen remains intact or may even be widened. When, however, the intima is involved, then the lumen is narrowed. In some cases, ulceration of the endothelium occurs, and is followed by thrombosis. Calcification or other degenerative changes in the walls of the arteries do not, in themselves, cause symptoms. It is when occlusive thrombosis occurs that symptoms develop.

In diabetic individuals the atheromatous type of lesion is the outstanding one, even in the muscular arteries, where it may occur alone or superimposed upon medial calcification. As a result the obliterative process not only tends to become apparent at a relatively early age, but there is likely to be an extensive involvement of small vessels so that compensatory development of a collateral circulation may be poor.

In contrast to thromboangiitis obliterans (Buerger's disease) arteriosclerosis is localized in the arteries themselves whereas in thromboangiitis obliterans the inflammatory process extends beyond the arteries to the accompanying veins and nerves. In arteriosclerosis obliterans, phlebitis and periarterial neuritis are not usually seen.

SYMPTOMS: DR. DONALD W. LEIK†

The first evidence of deficient circulation in an extremity is likely to be pain brought on by the use of that extremity. If the legs are involved and the individual steps out, he fails to obtain a sufficient blood supply for his laboring muscles, rests and sets out again, suffering in fact the intermittent claudication first described over a century ago in the case of the horse, by French veterinarians. Characteristically the pain is cramp-like and is felt in the calf, but variations from the usual picture are not uncommon. The affected region may be the sole of the foot, the instep, even the thigh. The complaint may be a dull ache or numbness. Moreover, in the upper extremity weakness may be more frequently the complaint than pain. Recognition of intermittent claudication is based on the relation to exercise. Any uncomfortable sensation in an extremity which is brought on by exercise and relieved by rest is intermittent claudication. It is angina of the legs. By contrast the pain of flat feet, or of venous stasis is worse when the patient stands still than when he walks about, whereas intermittent claudication is relieved by standing still. The pain of arthritis does not cease until the patient sits down.

The arteriosclerotic patient may describe another type of pain, one which comes on at night and awakens him out of sleep. This is probably the result of local ischemia which occurs when the systemic circulation is slowed during sleep. Relief is obtained by placing the painful extremities in a dependent position. Idiopathic nocturnal cramps may often be distinguished from the rest pain of arterial deficiency by giving the patient a single capsule of quinine before bedtime. This may relieve cramps but will not affect the pain of arterial deficiency.

Persistent, continuous pain in the extremities, especially in the toes and forefoot, may be the forerunner of impending gangrene. If such a pain appears suddenly, it usually signifies thrombosis of a major artery, and prompt treatment is called for.

Some patients may complain of coldness or blueness of the extremities. These symptoms are more likely to signify spasm of the vessels than organic

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occlusion. However, an association of vasospasm with arterial occlusion is not uncommon especially after a fairly recent thrombosis.

Physical Signs

The examination of the patient should be performed in good natural light at a comfortable room temperature. In starting the examination the physician should note atrophy of the skin or trophic changes in the nails. Hairless atrophic skin on the lower legs is frequently seen in arteriosclerosis obliterans. Skin color on the sole and dorsum of the foot should be observed in three leg positions: horizontal, elevated to an angle of 45 degrees, and dependent. Pallor may develop only after the legs have been elevated for two or three minutes and may be overlooked if the period of elevation is too brief. An excellent measure of inflow rate, which can be recorded accurately, is the time, in seconds, required for color return when the feet are placed in dependency from an elevated position. The characteristic dependent rubor of arterial insufficiency likewise requires several minutes for its full development.

Ulceration is not a rare result of arterial insufficiency. It tends to occur distal to the malleoli, in contrast to the ulcers of venous stasis which usually appear in more proximal tissues. In most instances these ulcers are exquisitely painful so that local treatment is difficult. At other times, in diabetic patients especially, one may be surprised to find almost no discomfort associated with a deep ugly-looking sore. Too often an ulcer on a toe due to arterial insufficiency is mistaken for an ingrown toenail.

Adequate examination should include not only palpation of the dorsalis pedis and posterior tibial pulses, but also the popliteal, femoral, radial, and ulnar pulses. Unfortunately, palpation of the arteries in the lower extremities is not part of most routine physical examinations. Yet, unless one is thoroughly familiar with the exact location of the normal pulses, it is impossible properly to interpret the apparent absence of pulsation in a suspected case of arterial insufficiency. Approximately ten per cent of normal individuals will exhibit a bilateral absence of the dorsalis pedis artery. Unilateral absence of the latter is suggestive of arterial disease, and absence of any of the other lower extremity pulses is definitely evidence of obliterative vascular disease.

The skin temperature can be estimated with the back of one's hand. In this way small differences in comparable areas may be detected and should be observed from the tips of the toes to the knees. Cold toes from which the temperature rises sharply toward the ankle or lower leg are more often associated with vasospasm than with arterial occlusive disease. One may even find relatively warm toes in a patient with no palpable arterial pulsation below the umbilicus. Finally, in examining a patient with peripheral arterial disease, a clinical estimate can be made of the degree of vasomotor activity. An individual with blue, moist, cold skin under which the superficial veins are constricted, has high vasomotor tone. If the skin is pink, dry and warm with prominent superficial veins, the vasomotor tone is low. With marked vasospasm the pulses about the ankle may be difficult to palpate but such active vasospasm may be relieved by immersing one or two of the other extremities in warm water at 110° F. for a maximum of 35 minutes.

From the viewpoint of prognosis rather than of therapy, it is desirable to determine whether peripheral vascular occlusion is due to thromboangiitis obliterans or arteriosclerosis obliterans, and if the latter, if it is associated with diabetes mellitus. Inasmuch as mild diabetes may not produce glycosuria, blood sugar studies should be performed in the presence of arteriosclerosis obliterans in individuals under 60.

The following table lists some of the criteria by which arteriosclerosis obliterans may be distinguished from thromboangiitis obliterans:

	Thromboangiitis Obliterans	Arteriosclerosis Obliterans
Onset	Rarely after 40	Rarely before 40
Sex	99% males	75% males
Upper extremity involvement	40% of cases	Rare
Migratory phlebitis	40% of cases	Never
X-ray evidence of calcification in arteries	None	Frequent

Prognosis

While arteriosclerosis obliterans tends to become progressively more severe, the progress is not uniform in rate, but rather seems to consist of a series of occlusive episodes often due to thromboses. Between these relatively acute episodes the patient's condition may remain static or even show improvement as collateral channels develop. However, at any time, even in the non-diabetic patient, a local infection arising in the poorly nourished tissues of the foot may precipitate gangrene. As a consequence, the therapy of this condition attempts to achieve two objectives: (a) Protection of the ischemic tissues from injury and infection; (b) measures to aid the development of collateral circulation. For a properly treated cooperative patient the outlook for survival of the affected extremities is good. In fact most of these patients will die from other manifestations of their arteriosclerosis, such as coronary occlusion or cerebral hemorrhage, without prior loss of an extremity.

MANAGEMENT: DR. THEODORE B. MASSELL‡

Personal Hygiene

The first problem in therapy is the regulation of his personal habits by the patient himself. From the beginning he must give up smoking. The weight of recent evidence is against the efficacy of such compromises as cutting down the daily cigarette ration, using denicotinized tobacco or filtered cigarette holders. A complete and permanent renunciation is necessary.

Dietary regulation is also indicated. A low cholesterol diet may slow the arteriosclerotic process and perhaps even cause some reversal in those individuals who manifest a hypercholesterinemia. For obese patients the low cholesterol diet may be included in a

‡ Chief of Vascular Surgery Section.

weight reducing regime. Most patients will understand the desirability of reducing the load to be borne by legs in which the circulation is impaired.

Good foot hygiene should become a habit. The feet should be bathed daily with mild soap and lukewarm water. Drying should be gentle but thorough, especially between the toes, and in these locations wisps of lamb's wool should be placed to prevent maceration. The patient should be taught to cut his nails straight across in a good light. In the older age group in whom vision may be impaired, the trimming of toenails should be done by a younger member of the family or a chiropodist. The services of the latter may be utilized also for shaving corns and calluses which might otherwise provide a source of fissures and ulcers. Trichophytosis should be rigidly controlled.

Both patient and physician must realize that extremes of temperature are to be avoided. Usually the discomfort experienced on exposure to cold results in the assumption of adequate protective clothing by victims of arteriosclerosis obliterans. Wool socks may well be worn year round and in cold climates fleece-lined shoes are advisable in the winter. On the other hand the danger of exposure to heat is too frequently not recognized. In a limb in which there is arterial stoppage the circulation may be just adequate to supply the metabolic needs of the distal tissues at a low level of activity. External heat causes a local increase in metabolic activity of the heated tissues, an increase which cannot be met by more blood flow through the already narrowed or obstructed arteries. The result of the disparity between blood need and blood supply may be gangrene. Consequently the physician must not only avoid the use of local heat (e.g. diathermy, infra-red, hot baths) in treating peripheral arterial disease, but he must warn the patient against self-treatment along that line.

Most patients soon learn from the pain occasioned by exercise that much activity is undesirable when the blood supply is inadequate. On the other hand mild exercise tends to stimulate the development of collateral circulation. Position also may affect the flow of blood into a limb in which the arteries are occluded. The night pain which disturbs the sleep of some victims of peripheral vascular disease may be relieved by the simple expedient of raising the head of the bed on blocks. On the other hand a victim of peripheral arteriosclerosis may develop gangrene merely because his physician treats a mild foot infection by elevating his leg on pillows.

Physical Therapy

It has long seemed plausible to treat peripheral arterial insufficiency by some form of physical therapy. Many ingenious types of apparatus have been devised for this purpose but the results on the whole have been disappointing. One of the oldest mechanical devices to improve circulation is the pressure suction (Paevex) boot. Despite the ingenious theory on which the machine is based, it seems to be ineffective.

Somewhat more recent is the intermittent venous occlusion apparatus or Burdick machine. Its purpose is to produce temporary intermittent obstruction to the venous outflow with the expectation that thereby the blood which flows into the extremity will be more efficiently utilized. In the intact limb reflex vasospasm probably nullifies the action of the passive vascular exerciser, but it may well be of some value when used on a sympathectomized extremity.

The effect of gravity on peripheral blood flow has long been the basis of Buerger's exercises. Unfortunately a patient would have to perform these exercises for many hours each day in order to derive any significant benefit. This routine is likely to be unacceptable even to those rare patients who might possess sufficient physical endurance for such therapy. With an oscillating bed the same effect may be obtained for 24 hours daily without any expenditure of energy by the patient other than that required to secure the money necessary to purchase or rent the bed. Even the ambulatory patient who is occupied by day, may derive benefit from sleeping in an oscillating bed.

Various ways of bringing heat to the body are used in physical medicine. For reasons already stated the local application of heating devices to the ischemic extremities is contraindicated. Heating other parts of the body will bring about a reflex vasodilation in the diseased regions. The limitations of vasodilator physical therapy will be considered with the vasodilator drugs.

Drugs

Physician and patient alike have long been hoping that some drug will be found to relieve the victims of peripheral arterial insufficiency. Too often this popular interest has led to flamboyant articles in the lay press in which bombastic claims for some newly developed medicine may even precede the reports in the medical literature. It is difficult for the physician to maintain his normal scepticism when he is confronted by an enthusiastic patient armed with an authoritative article on some new miracle drug taken from a digest magazine or the daily paper. Actually drug therapy has to date been the least effective form of treatment for peripheral vascular disease.

The majority of the drugs used have been vasodilators. These vary in efficiency but all have certain defects in common.

1. Any form of treatment which produces generalized vasodilation will have more effect in those parts in which there is no occlusive arterial disease than in extremities in which there is considerable obstruction to normal blood flow. So much blood is diverted to normal regions that relatively slight improvement occurs in the circulation of the arteriosclerotic parts. It has been well demonstrated that general vasodilation is much less effective than local vasodilation (as would result from sympathetic ganglion block) in increasing blood flow in an extremity with arterial disease.

2. The local circulatory improvement brought about by vasodilator drugs (or by physical therapy) is of brief duration so that the administration of the drug has to be repeated frequently and continued indefinitely.

3. When surgical sympathectomy has already been performed for peripheral arterial insufficiency, it has been demonstrated that the administration of a generalized vasodilator will cause a decrease and not an increase in blood flow through the sympathectomized extremity.

Despite their lack of therapeutic usefulness the catalog of vasodilator drugs is a long one. Two of the most recent additions are Etamon (tetraethylammonium chloride) and Priscol (benzazoline hydrochloride). A therapeutic dose of either of these is almost as effective as having the patient immerse his arms in warm water for 20 to 30 minutes. Farther down on the list are Padutin (vascormone), Depropanex (deproteinated pancreatic extract), nicotinic acid, and intravenous ether. These differ in the physiologic mechanism whereby they act, but have in common a lack of therapeutic effect. One of the most publicized of the vasodilator drugs is histamine, given as histidine and ascorbic acid. The lack of improvement which has been observed following this form of treatment could well have been predicted, since the dependent rubor of arterial insufficiency is the result of an excess of histamine (or a related substance) already in the poorly nourished tissues. If one wishes to use some vasodilator drug for arteriosclerosis obliterans, an ounce of alcohol by mouth three times a day is probably the best choice. Whiskey is a rather effective vasodilator of fairly sustained action, is not as expensive in therapeutic doses as most other vasodilator drugs, and to many patients it may even be enjoyable.

Other drugs have been suggested for the treatment of circulatory deficiency in the extremities which are not vasodilators, but which purport to alter the properties of the blood or the tissues. These include such remedies as tocopherol (vitamin E), sodium tetrathionate (tetrathione) and cytochrome C. Each has been announced with enthusiasm by its originator but there has been a dearth of confirmatory reports by subsequent observers.

Surgical Treatment

Within the last decade there has been a growing realization that arteriosclerosis obliterans may often be improved by the permanent release of vasoconstrictor impulses such as that which follows surgical sympathectomy. The persistent dilation of blood vessels which results from sympathetic nerve section seems to be a stimulant to the development of new collateral channels.

The injection of procaine into the sympathetic ganglia once or repeatedly does not duplicate the therapeutic effect of surgical sympathectomy, but a single procaine sympathetic block is a diagnostic procedure from which one can derive an approximate idea of the response to be obtained from a permanent sympathetic denervation. If a sympathetic block will relieve ischemic pain, increase a patient's tolerance for exercise, or convert a cold blue foot into a warm pink one, sympathectomy is indicated. Occasionally one may encounter a patient with low vasomotor tone who shows no apparent improvement in circulation following sympathetic block. Such a patient may be made worse by sympathectomy. Neither diabetes nor coronary artery disease is a contraindication for this operative procedure.

The injection of alcohol into the sympathetic ganglia is rarely justified as a substitute for sympathectomy because of the frequency with which the former is followed by neuralgia, paralysis or sloughing. In an emergency in which a sustained vasomotor paralysis is needed for a patient who is too sick to withstand operation, ten cubic centimeters of bromsalizol may be injected safely into the sympathetic ganglia to produce a block which lasts up to a fortnight.

Sympathectomy for arteriosclerosis obliterans should include the first lumbar ganglion as well as those below it. The sterility that usually follows bilateral loss of the first lumbar ganglion in the male is usually no problem in patients of this age group. On the other hand the chief source of arterial blood flow to the leg may be from collaterals which originate from the profunda femoris artery. These receive most of their vasomotor supply from the uppermost part of the lumbar chain. Lumbar sympathectomy does not contribute at all to impotence.

Another useful form of surgical therapy in peripheral arterial disease is local amputation of a toe. When a patient exhibits a chronic ulcer of a toe, perhaps with osteomyelitis of a phalanx, which does not respond to conservative management, it is advantageous to remove the entire toe through the metatarsal head. When the circulation is good at the operative site, the use of modern antibiotics permits a closed amputation. If there is doubt about the local circulation, an open operation is safer, with beveling of the wound to provide good drainage. Articular cartilage should never be left in place at the site of amputation.

In recent years the ligation of veins, such as the femoral or popliteal, has been pretty much discarded as a method of treating peripheral arterial insufficiency. It is now generally conceded that obstructing the outflow of tissue metabolites is rather illogical therapy for a condition in which most of the symptoms are due to an overaccumulation of these metabolites. Furthermore the edema that often follows ligation of a major vein may provide considerable embarrassment to the tenuous collateral circulation.

SUMMARY

Arteriosclerosis obliterans is the result of a common and more or less unpredictable pathological process, the end result of which is frequently occlusion of the arteries by thrombosis. The symptoms and signs are sufficiently characteristic so that the diagnosis can usually be established without any special equipment.

Treatment is symptomatic. The most important factors in good management are the regulation of the patient's personal habits and the proper use of such surgical procedures as sympathectomy and local amputation. Drug therapy is essentially of no value and physiotherapy is of only slight benefit.

Clinical-Pathological Conference

A white American bellboy, 50 years old, entered the hospital on January 2, 1948, with sore throat of nine days' duration.

The patient has always lived in the United States except for a seven-month trip to Alaska in 1943. He said that he consumed a moderate amount of alcohol. A brother had died of tuberculosis.

Present Illness: The patient was feeling well on December 1, 1947, when he went on a vacation to Blue Lake in Northern California. There he drank some raw milk. A few days later a head cold developed and it persisted. On December 25, 1947, after returning to San Francisco, he noticed a sore throat and began coughing up small amounts of white phlegm. These symptoms increased and he went to bed because of chilly feelings, headache, malaise, and generalized aching. The cough became productive of about two cups of white material daily. At the same time there were slight dyspnea and mild anterior chest pain. On December 28 diarrhea developed, with five to seven loose brownish-black stools daily, and mid-abdominal cramps. The patient ate little and lost about 15 pounds.

Although well developed, the patient was thin and appeared to be exhausted. He coughed intermittently. The temperature was 103° F., the pulse rate was 130, and respirations 32 per minute. Blood pressure was 100 mm. of mercury systolic and 65 mm. diastolic. The skin was warm and moist. The nasal mucosa was inflamed, with crusted exudate, and the soft palate and pharynx were highly injected and edematous. No abnormalities were found in the neck, and the lungs were clear to percussion and auscultation. The heart was not enlarged and the rhythm was regular. A soft systolic blowing murmur was heard along the left sternal border. The abdomen was soft and non-tender, and a soft, non-tender liver edge was felt 3 cm. below the right costal margin. There were no abnormalities in the extremities.

Examination of the blood showed a value for hemoglobin of 13 gm. per 100 cc. Erythrocytes numbered 4.2 million and leukocytes 4,500 with 34 per cent polymorphonuclear cells (26 per cent segmented and 8 per cent non-segmented), 60 per cent lymphocytes and 6 per cent monocytes. Corrected erythrocyte sedimentation rate was 24 mm. in one hour. The urine was normal. Results of a Wassermann test were negative. There was no growth on four blood cultures. Alpha streptococci and non-hemolytic staphylococci were identified in a smear from the throat. Studies of the blood for viruses, cold and heterophile agglutinins were negative, as were results of all agglutination tests. The feces were watery, green-yellow. No ova or parasites were seen in stool specimens either in the hospital laboratory or in the health department laboratory. A stool culture grew no abnormal organisms. Nothing of note was found in the sputum which was examined unstained and stained by both Gram and Ziehl-Neelsen methods. A roentgenogram of the chest showed no abnormality.

Course: The fever varied from 100.6° to 103° F. and the patient weakened progressively. Several loose green stools were passed but the main complaint continued to be sore throat. On January 9, leukocytes numbered 22,000, with 78 per cent polymorphonuclear cells (63 per cent segmented and 15 per cent non-segmented). Penicillin was given without apparent benefit. Repeat agglutinations done January 13, 1948, were positive for typhoid in a dilution of 1:80, but agglutinations the next day again were negative. On January 14, the patient complained of abdominal pain and that evening appeared much worse, with a pulse rate of 144 and no blood pressure reading obtainable. There was tenderness and guarding in the left lower quadrant which soon spread to the entire abdomen, with rebound tenderness. Peristalsis remained active. The blood pressure rose briefly to 90 mm. of mercury systolic and 50 mm. diastolic following intravenous injection of blood and fluids, but it soon fell again and the patient died on the morning of January 15.

From the San Francisco Hospital, May 11, 1948.

CLINICAL DISCUSSION

DR. EDGAR WAYBURN*: The course of illness in this patient may be divided into three major phases. The first begins early in December and lasts through most of that month. The chief symptoms are those of a systemic disease, presumably an infection (headache, malaise, chilly feeling, generalized aching), with partial localization to the respiratory tract as shown by the cough productive of as much as two cups of white sputum daily, dyspnea and chest pain. The second phase is revealed and spotlighted by the statement that on December 28 mid-abdominal cramps began, with diarrhea of five to seven loose brownish black stools daily. Shortly after this the patient entered the hospital. At this time he appeared rather severely ill for one who had developed symptoms less than a month before. The physical signs that he had lost a good deal of weight and was dehydrated and exhausted, offer no localizing clues. The laboratory data indicate that the staff was diligent and suspicious of a variety of conditions, and, further, that it was forestalled in its wide search by running into a number of dead-end negative tests.

At this point we may consider the various diagnostic possibilities, as they must have appeared to the attending staff, and where they seem to lead. We are confronted by a severe, subacute to chronic disease which appears to be advancing rapidly and which seems to have attacked both the respiratory and gastro-intestinal systems. The straw man which must be set up in diagnosis is typhoid fever. The onset and the course, the involvement of the respiratory as well as the gastro-intestinal tract are not unfamiliar. The low leukocyte count with a low per-

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centage of neutrophiles in the smear is an ancillary sign of value, as is the appearance of the stool. However, all of the confirmatory tests were negative repeatedly—the blood cultures, the stool cultures and the agglutination tests. (An agglutination test positive for typhoid in 1:80 dilution is without significance, particularly when others are completely negative before and afterward.)

The second disease to consider is tuberculosis, which may very well attack both the respiratory and gastro-intestinal tracts, as this disease did. Here again, all of the laboratory studies negate the historical data: The sputum and the roentgenogram of the chest are the two most important studies here. (In passing, one wonders how the patient could have so much cough, chest pain and sputum and still have a normal appearing roentgenogram of the chest as well as absence of physical signs.)

The third disease which deserves major consideration is amebiasis. The manifestations of amebiasis are protean and the symptoms may be respiratory as well as intestinal. There is nothing in the history or the physical signs of this patient which may not be caused by amebiasis. The laboratory test which could make the diagnosis—the microscopic examination of the feces—is negative, but amebae are all too often not demonstrated, even when special effort is made to find them.

Other conditions which one may consider are systemic fungus infection and regional ileitis, but neither appears very likely. Mention of the fact that raw milk was drunk reminds us that infected raw milk may cause brucellosis as well as typhoid, but brucellosis also appears unlikely.

The third phase of this patient's course began January 9, at which time the leukocyte count was 22,000 with 78 per cent polymorphonuclear neutrophiles. We presume that the blood examination was done at this time because of some change in the clinical status, although there is no mention of it. Whatever the change was, it caused the attending physician to administer penicillin, without apparent effect. Five days later, on January 14, the patient developed signs which suggest perforation of a viscus—or perhaps hemorrhage—followed by shock and peritonitis.

Whatever may be the primary diagnosis, I believe that we have the right to state that the terminal episode, the immediate cause of death, was perforation, probably of the intestine, followed by peritonitis.

To return to the primary diagnosis, we have a condition which has progressed rapidly and lethally over a known period of five weeks and which has involved the intestine in an ulcerative process which ends in perforation. I think that we may rule out tuberculosis first, for in order to have tuberculous enterocolitis of this severity and nature the patient would almost have to have pulmonary tuberculosis of sufficient chronicity and degree to cause indicative physical signs, sputum positive for tuberculosis and manifestations on a roentgenogram of the chest.

With regard to typhoid fever, one may say that the course of illness in this case was not typical of the average case of typhoid. However, in these days when typhoid is a sporadic disease, one sees more atypical than characteristic courses. The description of watery green-yellow stools rouses memories of "pea-soup" and the leukocyte count of 4,500 with 34 per cent neutrophiles fits no other disease quite so aptly. From there on, however, the result of every laboratory test is lined up against the possibility of typhoid. Cultures of the blood and of the stool were negative; one set of agglutination tests suggests agglutination in a dilution of 1:80—which is certainly doubtful in any case—but similar tests done both before and after this one are entirely negative. These are procedures which are performed commonly and which should have been positive sooner or later if the patient had typhoid.

Coming back to amebiasis: The only way to be positive of the diagnosis of this disease is to demonstrate the causative parasite in the feces or in the tissues. Stool examinations were negative in this case, but the demonstration of amebae is notoriously unsuccessful. Amebiasis would explain, better than typhoid fever, the pulmonary symptoms (of which the patient apparently complained more than the intestinal) which one could account for on the basis of multiple abscesses too small to be demonstrated in a roentgenogram. In this case ulcerative lesions in the intestine, with perforation of one of the ulcers, might be suspected.

Clinical Diagnosis: Amebiasis with perforation of intestinal ulcer.

DISCUSSION BY PATHOLOGIST

DR. W. W. MCLAUGHLIN*: The peritoneal cavity contained about 400 cc. of turbid yellow fluid and the peritoneal surfaces were covered with much patchy friable exudate. In the mid-portion of the transverse colon there was a 4 mm. perforation which was partly covered by adherent fatty tissue. This perforation was in the base of an ulcer which was deeply undermined. There were numerous ragged, "moth-eaten," often undermined ulcers measuring up to 2 cm. across in the colon which were characteristic of those produced by amebiasis. They were more numerous in the proximal portion of the colon; the sigmoid was not involved. Histologically, some of the ulcers had a typical flask shape and amebae were present.

The right lung weighed 650 grams. The lower lobe, hyperemic and edematous, contained patches of consolidation plus several ragged cavities.

There was fibrinous exudate over the pleural surface. The bronchi were hyperemic. Histologically, the pneumonia was found to be secondary to aspiration, with formation of multiple abscesses. This may well have been associated with the peritonitis, which may have preceded the pneumonia. The abscesses in the lung did not resemble amebic abscesses and did not contain amebae. Some of the changes in the right lung were old enough to have accounted for the respiratory symptoms noted clinically in late December. However, separate unrelated pneumonia at this time is another possibility. An incidental finding was healed cirrhosis of the liver.

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California Cancer Commission Studies*

Chapter XVIII

Cancer of the Breast

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EARLY breast cancer and late breast cancer are almost two different diseases. These differences are evident in the clinical picture, the plan of treatment, and the prognosis.

EARLY BREAST CANCER

1. SYMPTOMS. *There are none.* In all but a few cases, attention is first called to the breast by the *accidental* discovery of a lump which had previously given rise to no sensation whatever. In only about 1 per cent does pain or discomfort come first. So uniformly true is this that a woman who *finds a lump because of pain or tenderness* can almost be assured that she does not have cancer. Rarely, eczema of the areola or bloody discharge from the nipple are the first symptoms of cancer.

It is time to change emphasis in lay education. A quarter century of persistent publicity has taught women to seek medical advice promptly on the discovery of a lump in the breast. They now go to a physician within a week or two instead of waiting a year or more. Consequently the percentage of cases operated upon before axillary metastasis occurs has doubled or more than doubled. But it is unbelievable how large lumps can become before *accidental discovery*. All too frequently cancers have time to grow to walnut size or even larger before they are found.

Nor is the annual "check-up" a trustworthy assurance of early discovery. A cancer beginning just after one examination may well become incurable before the next year's visit to a doctor. We should teach women to feel their own breasts. Lying in bed or in the bath (not sitting, with the pendulous breast doubled over by its own weight) a woman ordinarily can feel the usual hard lump of cancer when it is no larger than a pea.

2. SIGNS. There are none, except the presence of a lump. The secondary signs of skin or nipple retraction are produced by the contraction of new connective tissue developing with the tumor, and this requires time. The very presence of these changes is proof that the cancer is no longer early. Pig-skin changes, ulceration, fixation to the chest wall, secondary skin nodules indicate even later disease. Palpable axillary nodes (unless large and hard or fixed) may be only inflammatory and so are unreliable as a sign of cancer. *In the earliest cases, when the prospect of cure is brightest there are no signs by which the lump of cancer can be distinguished with certainty from a benign lump.*

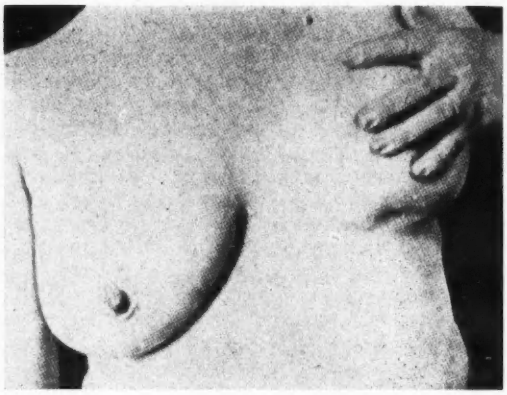

Figure 1.—Skin retraction produced by "traumatic fat necrosis"—indistinguishable from that of cancer. (Traumatic Fat Necrosis of the Female Breast and its Differentiation from Carcinoma. Lee, B. J., and Adair, F. E., Ann. Surg., 80: 1924: 670-690).

It is perhaps worth noting that even the late sign of skin retraction is not always pathognomonic of cancer. It has been observed over cysts in which there has been infection. And about half of the cases of innocent lipogranulomatosis (traumatic fat necrosis) will present skin retraction indistinguishable from that caused by cancer. (Figure 1.)

First, it is essential to determine that there is a lump. Areas of thickened breast commonly confuse patients and frequently confuse doctors. About half of the "lumps" that cause patients to seek medical advice prove to be such areas of thickened breast and not true lumps. In addition to examination sitting or standing, if the patient reclines with hands over head, and the breast is examined with the flat of the hand and not between thumb and fingers, such areas of thickened breast will usually "scatter" and lose their definition. It is worth while acquiring experience in order to make the distinction with assurance.

After it is determined that a true lump is present, no amount of further clinical examination will determine its nature. A clump of cysts can be as hard and as irregular in contour as any cancer. Cancer can even mimic the feel of an encapsulated adenoma or of a tense cyst. There is only one safe rule—*every single lump in the breast* must have its nature proved.

3. PROGNOSIS. Nothing so emphasizes the difference between early and late breast cancer as a comparison of "cure rates" based on amount of spread

*Organized by the Editorial Committee of the California Cancer Commission.

outside the breast which time has permitted. On average, these are about as follows:

Axillary Nodes Involved (pathologically proved)	Per cent of patients clinically well at five years
None	70
One	20-40
Multiple	5-10

4. EXPLORATION. Delay between exploration and radical operation for cancer of the breast substantially reduces chances of cure. This principle should by now be settled and universally accepted. *No physician should ever explore a lump unless he is prepared and able to do an immediate radical operation.* It is necessary that diagnosis be completed at the time of exploration. Frozen section facilities and competent pathological judgment should be available whenever any lump in the breast is surgically exposed.

Since even frozen section diagnosis is not always entirely conclusive and does consume at least some time with the patient waiting on the operating table, the surgeon who undertakes exploration of breast lumps can and should acquire sufficient experience to recognize the gross characteristics of the common lumps encountered:

(1) *The encapsulated* lump which can be shelled out with blunt dissection is usually one of the benign adenomas. It may be a lipoma, a dermoid cyst or other non-indigenous tumor. But, while cancers occasionally present a sharply defined margin without grossly visible infiltration, they are not truly encapsulated.

(2) *Cancer* is densely hard, cutting like sanded cartilage, with surface grayish (rather than the pure glistening white of normal breast), with dirty yellow or grey white streaks instead of healthy yellow fat, and fixed to if not actually infiltrating surrounding tissue. When sectioned the cut surface retracts, instead of bulging as does the adenoma.

All usual histological types of cancer present the same gross characteristics, except duct carcinoma spreading along duct spaces rather than forming a defined mass, and colloid or gelatinous carcinoma. A cancer 5 mm. in diameter has the same gross characteristics as one of walnut size.

(3) *Normal breast tissue.* The breast is composed of (a) gland structures—ducts and lobules—carried in (b) connective tissue stroma, padded with (c) fat. Gland structures in the inactive or atrophic breast are too small for naked eye recognition. But if ducts are dilated or lobules hyperplastic they may be recognized—the latter as grayish or flesh-colored, pinpoint to pin-head structures often very slightly elevated in freshly cut tissue. Breast stroma is a glistening white connective tissue, extremely flexible and compressible (so much so that it is almost impossible to cut blocks for sections until fixed).

The relative amounts of stroma and fat vary greatly from center to periphery of the same breast, with age and habitus of the individual, with phase of menstrual cycle, etc. But the stroma and fat elements are recognizable in non-tumorous breast tissue and hyperplastic lobules or dilated ducts.

(4) *Cystic disease.* (a) *The simple cyst* with "blue dome" before opening, with cloudy but non-bloody fluid, with smooth wall and normal breast tissue around it is often single but frequently multiple.

(b) *Hyperplastic or papillary cystic disease* presents a confusing variety of pathological pictures. There may be a single cyst or clump of cysts containing papillomata, or an entire breast may be filled with larger and smaller cysts. Areas may show hyperplastic ducts plugged with their overgrown epithelium so as to leave almost no recognizable normal breast tissue. It is this form of cystic disease, fortunately uncommon, which presents greatest difficulty in gross diagnosis. But it presents difficulty in frozen section diagnosis as well (and sometimes even in diagnosis with the best of paraffine sections). When it occupies a large part or all of a breast, it is the one condition for which a radical operation must occasionally be done without certainty that cancer actually exists.

When it comprises only a local area, however, it can usually be distinguished from cancer. And in the single papillary cyst, examination of the base of the papilloma will disclose presence or absence of the previously mentioned characteristic features of carcinoma.

Frozen section diagnosis is not always finally correct. Sections are seldom as well fixed, cut and stained as by good paraffine technique and it is possible to miss the "business part" of a specimen in hurried frozen section examination. The gross appearance is frequently sufficient and may occasionally be more reliable than frozen section. It should be studied at every breast exploration.

THE OPERATION FOR CANCER

The standard radical operation is based upon (1) the lymphatic anatomy (Figure 2)—drainage to the deep fascia, both directly and by a surface plexus communicating with the deep fascia lymphatics over the margin of the breast, or drainage to the axillary lymphatics both around and *through* the pectorals and (2) the tendency of breast cancer to spread by solid growth along lymph-channels. The purpose of the operation is to remove as much tissue into which cancer may have spread as may be done without an operative mortality (or morbidity) out of proportion to "cure rate." It consists in removal of the breast and its overlying skin, of the deep fascia from mid-line to posterior axillary line and from sternoclavicular joint to upper abdominal rectus, both pectorals (except the clavicular bundle of the major) and the lymphatics about the axillary vein (with the fat in which they lie). All this tissue is removed *in one mass* to avoid opening cords of cancer which may be growing in lymph channels. (Figure 3.)

This should be the minimum operation for any cancer, however small. Size of primary tumor is no indication of extent of spread. Still more extensive procedures—resection of clavicle and neck dissection, even shoulder girdle amputation—have been proposed for selected cases. But general opinion is

that the questionably increased "cure rate" resulting is insufficient to justify the increased mortality and morbidity.

Whether the operation is done with cold knife, cautery or electric current dissection is a matter of the surgeon's choice. The extent of actual cauterization is small and if cutting is done so close to cancer it might as well not be done. Usefulness of cautery or electric cutting is in reducing blood loss and operating time.

RADIATION SUPPLEMENTING SURGERY

There appears to be generally growing conviction that routine irradiation before or after operation adds little if anything to percentage of "cures." A course of irradiation planned to sterilize cancers is a very major procedure. Many patients subjected to it have volunteered that they would prefer suicide to a second similar experience. Nor is such treatment without risk of substantial and lasting ill effects—pulmonary fibrosis, cartilage necrosis, brachial neuritis, peri-articular fibrosis with stiffening of the shoulder. Without substantial gain in "cure rate" over operation alone, routine pre-operative or post-operative irradiation seems unjustified.

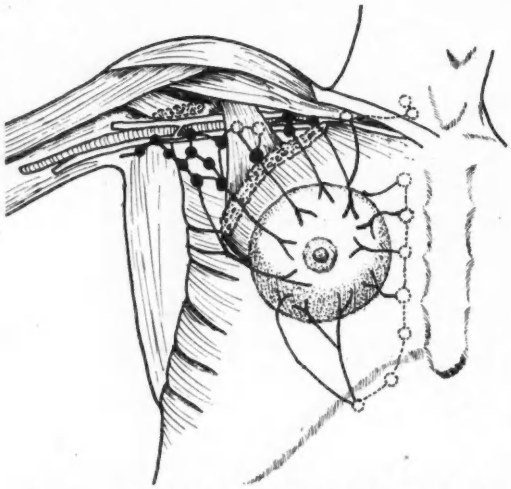

Figure 2.—Diagram of lymphatic drainage routes from breast—(1) to axilla *through* as well as around *both sides* of the pectorals (and "Wainright's gland" between the two muscles)—(2) via deep fascia to the intrathoracic internal mammary chain—(3) to abdomen via rectus fascia.

CYSTIC DISEASE AND CANCER

Unless one regards a normal breast as a "precancerous condition" and removes all whose owners will hold still (at, say, 45) he should not delude himself and be dishonest with his patients by advising mastectomy because of the presence of abnormalities which are no more likely to produce cancer than is normal breast.

Such is the "blue-domed" cyst, single or multiple. Once its nature is established, it (and all its associated smaller cysts) may be let alone so far as safety is concerned.

The much less common (1:10) form of cystic disease characterized by extensive papillary and solid epithelial overgrowth has been the subject of more debate than any other breast disorder. Opinion has varied from regarding it as equally as harmless as simple cysts to the belief that it frequently produces cancer. This author's opinion is that the true facts lie between the extremes—that grossly demonstrable hyperplastic cystic disease is somewhat more prone to malignant degeneration than is normal breast. Therefore, he believes that so much of breast tissue as shows this form of cystic disease in its gross characteristics should be removed for protection—whether removal involves an intraductal papilloma, a single papillary cyst or clump of cysts, a localized area of diffuse change or even the entire breast if extensively involved.

NIPPLE DISCHARGES AND EROSIONS

Non-lactating duct mouths are normally closed with a plug of desquamated epithelium. If such a plug be dislodged, fluid present in ducts appears as a discharge and is without significance. It may vary from watery or creamy to green or brown and may come from several ducts.

If the discharge contains blood, however, it invariably indicates intraductal disease of some kind. Gross appearance of the fluid cannot be trusted to determine presence or absence of blood. Dark brown fluid, leaving stains on clothing like dried blood, may be innocent. Clear watery fluid may contain red blood cells. *Microscopic examination is required of all nipple discharges.*

In perhaps 90 per cent of cases of bleeding from the nipple, the source is one or more benign intraductal papillomata, while in the rest it comes from carcinoma. The ratio of cancers to papillomata increases, however, with advancing age. Some authorities have estimated that, in women over 50, bleeding comes from cancer in nearly 50 per cent. The source of bleeding must, therefore, be determined and appropriately dealt with.

Bleeding papillomata may be located anywhere in the breast but are most common in the larger ducts beneath or at the edge of the areola.

If a lump is palpable, it is explored and dealt with in accordance with its character.

More commonly, no lump can be felt, since the papilloma is too soft.

Transillumination may, by a dark shadow, show the location of a pool of blood about a papilloma. In this author's experience, it has been of infrequent help.

The location of the discharging duct mouth over the nipple may suggest the quadrant in which the papilloma lies.

Gentle pressure with finger-tip on successive points about the areola may indicate the source as discharge appears at the nipple. Other more precise methods failing, excision of a zone of breast about such a point has occasionally been successful.

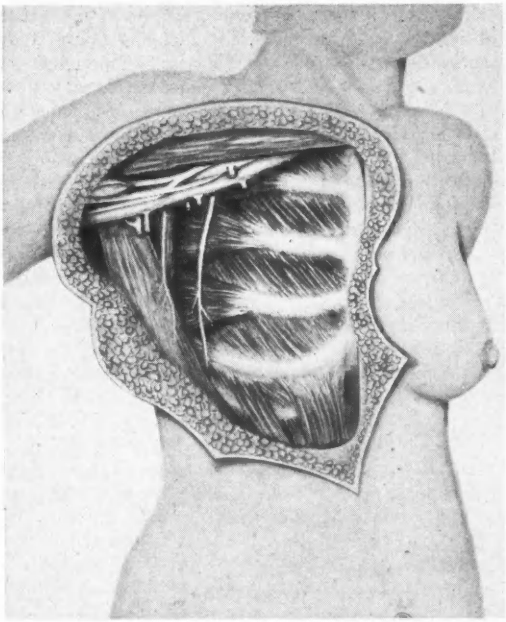

Figure 3.—Extent of removal of tissue by radical mastectomy. (From Lewis' Practice of Surgery, W. F. Prior Co., Vol. V, Chapter 6).

A very useful procedure is to milk a tiny drop of discharge to identify the duct, introduce the eye end of a small cambric needle as a probe, and split the duct on the needle as a guide until one or more papillomata are exposed.

Rarely the source cannot be located. A safe course to follow would be as follows: if the patient is a young woman, repeated observation will eventually reveal the source. If the patient is elderly, a simple mastectomy with immediate careful examination of the entire breast is indicated, since about half may show cancer.

Erosion or eczematoid conditions of the nipple, however small, which *do not yield promptly to conservative treatment*, virtually always come from intraductal disease, either cancer or precancerous hyperplasia. They require at least simple mastectomy—radical operation if cancer be found. The association of duct cancer with Paget's disease of the nipple, even in the absence of palpable underlying disease, is so constant, that *the diagnosis of Paget's disease demands radical mastectomy.*

LATE CANCER

Skin or nipple retraction, direct skin involvement or ulceration, "pig-skin," secondary skin nodules, large and hard axillary nodes and demonstrable distant metastases are clear evidence that the cancer is no longer "early." The problem is no longer one of diagnosis but of whether the disease is beyond even a small chance of cure by surgical operation. To subject a certainly incurable patient to radical operation does not prolong life, offers little or nothing of palliation and reflects discredit on operation for breast cancer. And, although perhaps not subject to statistical proof, clinical impression suggests that patients with incurable cancer do less well following radiation therapy if they have been operated upon.

It is this author's conviction that *surgically incurable cancer cannot be made surgically curable by irradiation*, however much the clinical appearance may be changed. If it is incurable in the first place, this is because cancer has spread beyond the field of radical operation. If cancer could be sterilized outside this field, it could be sterilized within it and there would be no reason for operation. If it cannot be sterilized outside the field of operation, operation will not cure it.

On the other hand, much relief (even an occasional "cure") can be offered by irradiation for inoperable cancer.

Each cancer of the breast should be surveyed in the first instance for surgical curability. Operations should be done for early cancer and even more advanced cancers not demonstably incurable. Surgically incurable cases should be selected for irradiation and *this method of treatment adhered to* throughout management. The only possibly useful surgical treatment is an occasional simple mastectomy to remove a primary mass too bulky for irradiation or to prevent or relieve ulceration of tumors proved insensitive to irradiation.

What signs are factors in the determination of curability?

Surgical cure may still be possible in the presence of the following signs:

1. Skin or nipple retraction.
2. Local skin involvement and ulceration. Some cancers—colloid for example—may reach large size and ulcerate before metastasizing.
3. Small movable axillary nodes.

Diagnosis of axillary metastasis by palpation is notoriously inaccurate. About a third of palpable nodes prove innocent; and in about the same proportion of cases, metastases are found pathologically even though no node was felt before operation.

Surgical cure is considered impossible and the patient should not be operated upon when the following signs are present:

1. Large, hard, fixed, axillary nodes. In these cases metastasis is a certainty. When metastasis has extended in a chain of nodes to the upper limit of an operative field, the probability of metastasis beyond the limits of surgical operation in the same or in other directions is overwhelming. In the author's experience, the presence of one hard fixed node, 2 cm. or more in size, indicates multiple node involvement and it is his conviction that such cases are surgically incurable.
2. Supraclavicular metastasis.
3. Pig-skin changes, extensive skin edema and secondary skin nodules. These are clear evidence of extensive involvement of lymphatics.

4. Distant metastasis. It is advised that chest and bone roentgenograms be made, the latter to include skull, spine, pelvis, humeri and femora. Evidence of metastasis, of course, precludes radical mastectomy.

5. Inflammatory cancer, a very rapidly growing, highly malignant cancer, usually in younger women. The whole breast is "frozen" early in the disease, the skin red, edematous and hot. It is uniformly fatal. Operation is useless. Even the needle punctures of ill-advised attempts to aspirate may start ulceration.

SIMPLE MASTECTOMY FOR CANCER

In feeble, aged women mastectomy to remove cancer from attention and worry may occasionally be justified. Very rarely it may be desirable to relieve an incurable patient of an ulcerating mass *proved radioresistant. In the usual treatment of breast cancer, simple mastectomy has no place.* Very early metastasis cannot be demonstrated clinically. With very early metastasis there is still a chance of cure by radical operation and no chance if the metastases are left.

Simple mastectomy plus irradiation as a standard treatment is without logic. If radiation could be depended upon to sterilize cancer outside the breast, it could sterilize it even more readily within the breast and no surgical operation would be necessary.

HORMONE THERAPY

There is as yet no general opinion and accepted practice concerning the use of hormone therapy in the treatment of breast cancer.

Surgical castration or ovarian irradiation has been followed by relief of pain from, and recalcification of, bone metastases. Adair has stated that improvement occurs in about 13 per cent of cases but that prophylactic ovarian irradiation does not reduce incidence of bone metastases. It does not cure the disease and does frequently add sudden severe menopause symptoms to a younger woman's discomfort.

Testosterone has been reported upon by a number of authors with varying conclusions. Adair finds that, given in large doses, it has favorable effect on bone metastases—both pain relief and recalcification. He suggests 100 mg. testosterone propionate intramuscularly three times a week for ten weeks followed by 40 to 60 mg. methyl testosterone by mouth daily for eight weeks. In such amounts it is likely to produce masculinizing effects and is certainly expensive. It would seem perhaps that the chief usefulness of both ovarian irradiation and testosterone will be found in the presence of bone metastases insensitive to direct irradiation or when no more irradiation can safely be given.

More recently, a number of reports indicate that stilbestrol in women well past the menopause may yield remarkable regression, especially of soft tissue lesions. No standard dosage can yet be laid down. Recommendations vary from 1 to 2 mg. up to 15 mg. daily. Even larger doses have been given without apparent ill effect (except recurrence of uterine bleeding, subsiding after withdrawal).

SUMMARY

1. Most breast cancers are discovered accidentally as painless lumps. They should be found earlier by intentional search.

2. Clinical examination should determine the presence or absence of a true lump. It cannot safely distinguish between benign and malignant lumps.

3. At exploration, frozen section facilities should be available and immediate radical operation done for cancer.

4. Blood-containing discharge from the nipple indicates either cancer or a precancerous lesion. Its sources must be established and dealt with.

Cancer of the Bladder, by A. J. Scholl, M.D., and Cancer of the Prostate by R. A. Barnes, M.D., Chapters XXIV and XXV of the California Cancer Commission Studies, will be published in this section in the December issue of CALIFORNIA MEDICINE.

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EDITORIAL

Banking on Blood

The value of blood as a therapeutic agent is so universally recognized today that scientific argument on it has ceased. On the other hand, the means and methods of obtaining and distributing human blood and blood derivatives continue to form the basis for much argument that is not all scientific.

Present-day discussion along these lines extends from coast to coast and border to border. A variety of opinions emerges, each type attracting its own adherents, but the basic question appears now to come down to about this: Should blood be distributed gratis by publicly-supported social agencies or should it come from self-supporting non-profit organizations which contribute scientific control and are largely in the hands of the medical profession? This question has been highlighted in the past year by the entry of the American Red Cross upon the blood banking scene. The Red Cross has adopted a national policy of fostering blood banks in all major cities of the country for the collection and distribution of blood, without charge, to all who may need it.

The possibility of disrupting established community non-profit blood banks has been seen by the Council of the C.M.A. in the Red Cross program. It has been discussed in the A.M.A. House of Delegates. The discussions resulted, early this year, in the appointment by the C.M.A. Council of a Blood Bank Commission, composed of members known for their interest in and knowledge of modern blood banking methods. This commission has actively worked toward the establishment of blood banks at the community level in strategic California cities and has achieved a large measure of success in its first few months of operation. The commission has discovered throughout the state a lack of knowledge of the underlying considerations of the Red Cross program as compared with the non-profit approach which has been so successful in this state.

Because the following progress report made by Dr. John R. Upton, chairman of the Blood Bank Commission, raises questions that will arise in your own community one of these days, if they have not already done so, it is highly recommended reading.

* * *

"A long range blood bank program has been planned for the State of California. If it is to be carried through, a full understanding of the present blood bank system is necessary. To this end, the following summary of pertinent facts:

"At present there are blood banks of five different types operating in the state. There are seven community or non-profit banks, eight county hospital banks, sixteen banks in private hospitals, several privately owned banks run for profit, and at least four in which the Red Cross is interested and from which blood is dispensed free of charge.

"In 1946 the California State Department of Public Health appointed a committee to study the blood coverage requirements of the State, to suggest a plan of action, and then to write a bill for presentation to the State Legislature. Representatives of the California Medical Association, county medical societies, community blood banks, osteopathic surgeons, Hospital Conferences, and California State Nurses' Association were interviewed. An excellent survey of the state was made by the Department of Public Health. Out of the long and exhaustive meetings

came Senate Bill Number 1257. This bill was presented to the Legislature in January of 1947 and was defeated. By its defeat, the State Blood Bank Program was set back at least three years.

"Basic principles of the bill were: The Department of Public Health would sponsor and aid in the establishment of community blood banks in areas which required the service. Operation and control of the banks were to be vested in the local county medical society. A maintenance, or service charge, was to be made for blood, and the blood would be replaced by a relative or friend of the person receiving it. Operating standards were to be set and maintained by the State Department of Public Health in accordance with regulations set forth in the Biologics Act.

"If the bill had become law, a tremendous stimulus would have been given local medical societies to establish community blood banks. When the bill was defeated, the Red Cross, cognizant of the dramatic aspects of blood banking, quickly entered the picture. The aim of the American Red Cross was to provide 'free blood for all.' This, their early slogan, was a most cruel misrepresentation of fact, for the plan called for the expenditure of 20 million dollars a year. You and I are the Red Cross. We have maintained (Editorial, CALIFORNIA MEDICINE, November, 1947) that a medical program such as blood banking is beyond the proper scope of the Red Cross. We stoutly believe that the recipient of blood should pay the small processing charge and provide a donor to replace the unit of blood which he received. The Bank should be self-supporting; it should be a community bank. Because years of experience have taught us the difficulty of getting even relatives and friends of the recipient to donate their blood, we cannot see how the Red Cross can indefinitely expect large numbers of people to donate for total strangers. A modern blood bank program is a far cry from the Red Cross blood procurement set-up of war days. The Red Cross centers then just drew blood from donors. The laboratory work, such as typing, Rh studies, and serology, was all done by commercial laboratories. The Red Cross Blood Program was a project well performed, but to try to change a war measure into a peace-time function and to expand that service into a full scale medical program is not within the province of the Red Cross.

"For the sake of the record, we emphatically state that our one main point of controversy with the American Red Cross is its demand that the patient shall not be required to pay a service charge for the blood received or to assume any moral responsibility for replacing the blood used. It goes without saying that no one has been or will be deprived of blood because of real inability to pay a service charge or to provide replacement. But aside from that, who *should* pay for the bottle in which the blood is stored, the rubber tubing, the needle, and the tests of serology, typing and Rh factors, and the salaries of technical personnel—for all the varied and intricate steps and checks that make for 'guaranteed blood?' Shall the recipient pay the modest non-profit service charge or shall strangers be asked to carry this financial load by their annual donations to the Red Cross?

"Efforts to get the American Red Cross to compromise this basic issue of the service charge and donor replacement have been to no avail, although many local Red Cross chapters are in full accord with our principles and would be happy to work harmoniously with the local county medical societies and their community blood banks. This willingness has been thwarted by the National Chapter, and to make matters worse the local chapters of the Red Cross were forbidden to aid in the 'permissive' program. We would welcome the participation of the Red Cross in the blood bank field if it would modify the socialistic features of its program. We would welcome its assistance in procuring donors, staffing canteens, and distributing blood on call to hospitals. The Red Cross can have the publicity; Medicine wants to give service. Our state-wide plan could well use the facilities of the local Red Cross chapters; they, in turn, would once more receive the necessary moral and ethical support of the medical profession. Each agency requires the enlightened and enthusiastic support of the other. The original premise of the Red Cross is to bring succor to the needy in time of emergency or disaster; that same, but greatly expanded, humanitarian principle has been espoused by the medical profession since its earliest beginning.

"When Senate Bill 1257 was defeated by short-sighted interests, the California Medical Association Council felt morally obligated to help. Its only interest in the Blood Bank Program is to see that people of the state are provided with adequate blood coverage. The plan of action is identical to that outlined in the defeated Public Health Bill. We stress the same fundamental points: the Public Health Department will maintain standards; the local county medical societies will operate and control the blood banks, and these banks will be supported by those who use the transfusion service.

"There are approximately 36,000 hospital beds in California. It is well established in medical statistics that approximately 180,000 units of whole blood per year is needed to serve that number of beds. (Five units of blood per bed per year is the amount required when adequate facilities are available and when the entire medical profession is fully cognizant of the therapeutic value of blood and its various derivatives.) Forty-six of the state's fifty-eight counties have little or no access to blood for transfusions. This woeful discrepancy must and will be corrected. Regional community blood banks are badly needed right now throughout heavily populated areas such as Los Angeles, Fresno, Bakersfield, and Santa Barbara. Just to mention a few potential sites, smaller banks might well be supported in Redding or Chico, Visalia and Ventura. Sacramento opened its community bank in October; members of the Sonoma County Medical Society assessed them-

selves in order to underwrite a similar bank in Santa Rosa.

"Many people still think that blood banks are needed only during a war, that only war's wounds require blood transfusions. That thought is entirely erroneous. Democracy's battlefields have, in the past, been her highways, her farms, and her great industrial plants.

"What of the future? What of the medical problem posed by just two recent developments, supersonic speed and the atomic bomb? Blood and blood plasma will form the therapeutic keystone in the treatment of casualties when and if a Hiroshima occurs in this part of the country. Adequate blood coverage for the state, high standards of service, coordination of all banks, reciprocity between banks, similarity of blood banking procedures, fast and efficient distribution systems, adequate mobile units geared to serve inaccessible areas, auxiliary substations, walking blood banks—these and many other problems present themselves for speedy and precise settlement. These are medical problems of the medical profession.

"We must gird for the long tasks and work together for the common weal. Let's get on with the job. Tomorrow may be too late. The solution rests with organized medicine. Why should not California have its own state-wide blood bank program, sponsored, implemented and operated by physicians?

"JOHN R. UPTON, M.D.,
"Chairman, C.M.A. Blood Bank Commission."

Letters to the Editor . . .

Tuberculous Lympholysis

It was shown by Rich,[5] Heilman[3] and others that splenic explants from tuberculous animals are killed when grown in concentrations of tuberculin that are harmless to normal tissue explants. Meyer[4] found that this hypersusceptibility is not a manifestation of classical anaphylaxis, since explants from animals sensitized to horse serum are not injured by the addition of horse serum to the culture fluid.

Detailed study of this cellular hypersensitivity is reported by Favour[1] of the Rockefeller Institute. Tuberculosis was produced in mice and guinea pigs by subcutaneous or intravenous injection of six to ten-day-old cultures of tubercle bacilli. Mice surviving three to four weeks and guinea pigs surviving two to six months were selected for cytologic study.

Suspensions of guinea pig lymphocytes, monocytes and granulocytes were prepared from pooled blood samples by the cell fractionation technique suggested by Ferrebee and Geiman.[2] This fractionation is based on the different specific gravities of different white blood cells, and their centrifugation from suspensions in standard dilutions of bovine albumin. A similar technique was used in fractionating suspensions of mouse splenic cells.

Toxic effects were demonstrated by adding 0.2 cc. cell suspension to 0.2 cc. dilute tuberculin (or other bacterial extract, such as S. enteritidis extract) in 0.5 cc. albumin solution. Lytic effects were measured by the resulting reduction in differential white cell count at the end of 60 to 90 minutes. In a typical experiment a suspension of splenic cells from a tuberculous mouse was reduced from an initial white cell count of 15,890 to 12,680 by 60 minutes' exposure to dilute tuberculin. Differential counts showed that this reduction was due to a 56 per cent reduction in lymphocytes unaccompanied by a loss of other cell types.

In a second experiment there was by the end of 90 minutes a 36 per cent lysis of lymphocytes from a tuberculous guinea pig, with no distinction of other cell types. Lymphocytes from normal mice or guinea pigs or from animals infected with S. enteritidis were not lysed by the same concentration of tuberculin. Lymphocytes from animals infected with S. enteritidis, however, were specifically lysed by soluble substances derived from cultures of S. enteritidis. Control tests with lymphocytes from normal or tubercular animals were not lysed by any extract thus far tested. Tubercular lympholysis can also be demonstrated in fresh heparized mouse or guinea pig blood to which tuberculin is added.

No theory is as yet proposed to explain this acquired specific lymphocyte hypersensitivity. Conceivably it is due to a specific activation of autolytic enzymes, a futuristic theory of possible clinical interest.

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NOTICES AND REPORTS

Executive Committee Minutes

Tentative Drafts: Minutes of the 210th, 211th and 212th Meetings of the Executive Committee of the California Medical Association.

The meeting was called to order by the Chairman at the Family Club, San Francisco at 7 p.m., Wednesday, July 21, 1948.

Roll Call:

Present were President Askey, President-Elect Kneeshaw, Speaker Alesen, Council Chairman Bruck and Auditing Committee Chairman Shipman, Chairman of the Executive Committee. A full committee present and acting. Ex-officio member present: Secretary-Treasurer Garland. Ex-officio member absent, Editor Wilbur.

Present by invitation were Doctor Dwight H. Murray, Chairman of Committee on Public Policy and Legislation; Doctor C. K. Cooley, secretary of California Physicians' Service; Mr. Ben H. Read, executive secretary of the Public Health League of California; Mr. Clem Whitaker, Public Relations Counsel; Mr. Howard Hassard, Legal Counsel, and Mr. John Hunton, Executive Secretary.

1. *Selective Service:*

A letter from Governor Earl Warren of California was read, in which he requested that physicians in various areas of the state be selected for appointment to medical advisory boards under the new Selective Service Act. The appointees would be called upon to review cases where manifestly disqualifying conditions were claimed by potential draftees, the armed services performing their own induction physical examinations. On motion duly made and seconded, it was voted that the county medical societies in the areas involved be asked to nominate physicians for such appointment.

2. *C.M.A. Constitution and By-Laws:*

It was pointed out that the 1948 House of Delegates had approved a resolution calling for the appointment of a five-member committee to review the Association's Constitution and By-Laws. On motion duly made and seconded, it was voted to refer this matter to the Chairman of the Council, which body should consider the Chairman's recommendations for such appointments at its next meeting.

3. *State Department of Public Health:*

Doctor Bruck reported that he, acting as a member of the committee to study chronic diseases for the State Department of Public Health, had declined to send to the secretaries of the county medical societies a letter which he believed to contain leading questions. Instead, a modified version of this letter, prepared by a representative of the State Department of Public Health, had been sent; however, the original letter had been sent to county health officers by a county health officer who is also a member of this study committee. It was agreed that copies of both letters should be sent to all members of the Council so that they could see the approach being made on this question. (Copies of both letters are attached hereto and made a part of these minutes.)

The recent action of the American Public Health Association in appointing a committee for the creation of a section on medical care was discussed and it was regularly moved, seconded and voted that the American Medical Association be requested to secure adequate representation at meetings of the American Public Health Association.

4. *California Society for Crippled Children-Epilepsy Program:*

Doctor Bruck reported that further conferences had been held with representatives of the California Society for Crippled Children and that a definite program appeared in the making, with the proposed case-finding program to be abandoned and with the county medical societies to handle the program in their own areas. A further report is to be made to the Council.

5. *Public Policy and Legislation:*

Doctor Murray reviewed some of the measures which will appear on the November general election ballot as initiative measures and placed particular

emphasis on the so-called "Bill of Rights" or "Omnibus" proposition, No. 11. He pointed out that this bill would create a board of naturopathic examiners which would thereafter control the licensing of all practitioners in all the healing arts. It was brought out that a taxpayer's suit has been filed against the Secretary of State to prevent this measure's appearing on the ballot and that the C.M.A. had been asked to appear as a friend of the court in the matter. After discussion it was regularly moved, seconded and voted that legal counsel be authorized to appear on behalf of the Association in this case.

6. *California State Chamber of Commerce:*

A request from the California State Chamber of Commerce to contribute $1,000 to the Chamber's work was read and it was regularly moved, seconded and voted that the Association make such a contribution this year.

7. *California Physicians' Service:*

Doctor C. L. Cooley, secretary of California Physicians' Service, reported that C.P.S. is now operating in the black and the present reserve in the unit stabilization fund is about $360,000. He also reported that C.P.S. is dealing with the Veterans Administration relative to a new VA regulation which holds that preliminary examinations to determine service-connected disabilities may not be paid for unless prior authorization from the Administration has been received. This regulation would mean that the first call on physicians by eligible veterans would not be paid for, and C.P.S. is endeavoring to secure its repeal. He also stated that the C.P.S. board of trustees has taken over as its own sub-unit the fee schedule committee headed by Doctor William L. Bender and originally appointed by the C.M.A. Council.

8. *Veterans Administration:*

The Secretary reported that the Veterans Administration was considering setting up a diagnostic center in Sacramento and another in Stockton, presumably for all examination of veterans claiming disability ratings but so laid out that full diagnostic and treatment facilities might well be made available. After discussion it was regularly moved, seconded and voted that it be the opinion of the Executive Committee that adequate machinery exists for the examination and rating of veterans claiming disabilities and that the county medical societies be encouraged to oppose the establishment of such local diagnostic centers as superfluous and unnecessary.

9. *Legal Department:*

Mr. Hassard reported that the Association of California Supervisors had met in July and had adopted a resolution calling for the recognition by county boards of supervisors of the shortage of hospital beds and the attempt by such boards to secure state and federal funds in aid of hospital construction. This would mean the competition of county hospitals with non-profit voluntary hospitals and a disadvantage to the latter in attempts to secure public funds for expansion. Mr. Hassard reported on a letter received from a member who has opened a pathological laboratory in association with other physicians who refer their work; the laboratory has been incorporated and the question of the ethics of such a procedure was raised. It was regularly moved, seconded and voted that this matter be referred to the next meeting of the Council and the physician be advised that the entire matter of such ethical considerations was under study; it was agreed to recommend that a full code be prepared on the ethical approach to the rebate question.

10. *Proposed Hospital-Radiologist Contract:*

Mr. Hassard reported that a committee of the Association of California Hospitals had reviewed the recent opinion of the State Attorney General, in which it was held that hospitals employing physicians on a salary basis were violating the corporate practices sections of the medical practice act, had recognized the validity of this opinion and had been instructed by that association to proceed with the drafting of standard types of contracts between hospitals and physicians to cover the rendering of professional services in hospitals. Doctor Garland presented a specimen contract which he proposed be used as a base for the variety of contracts needed in such cases and it was regularly moved, seconded and voted that legal counsel be authorized to discuss with the committee and legal counsel for the Association of California Hospitals the drafting and adoption of standard type or types of contracts to cover the rendering of professional medical services in hospitals.

11. *C.M.A. Employees' Retirement Plan:*

Doctor Alesen reported that the committee to consider a pension retirement plan for Association employees had approved a type of insurance contract offered by the Northwestern Mutual Life Insurance Co. There was discussion as to the number of employees to be covered by such a program and it was agreed that the matter be discussed further at the next meeting of the Council.

Adjournment.

SIDNEY J. SHIPMAN, M.D., *Chairman.*
L. HENRY GARLAND, M.D., *Secretary.*

211th Meeting

The meeting was called to order by Chairman Shipman at 6 p.m., Sunday, August 22, 1948, in Room 210 of the Sir Francis Drake Hotel, San Francisco.

Roll Call:

Present were President Askey, Speaker Alesen, Council Chairman Bruck and Auditing Committee Chairman Shipman, chairman. Absent, President-Elect Kneeshaw. Present by invitation, Legal Counsel Hassard.

A quorum present and acting.

1. *Time and Place of Annual Secretarial Conference:*

After discussion it was regularly moved, seconded and voted that the annual Secretarial Conference be held in San Francisco on February 4 and 5, 1949.

2. *Appointment to C.P.S. Fee Schedule Committee:*

It was regularly moved, seconded and voted that Doctor Herbert J. Kirchner of Los Angeles be appointed a member of the C.P.S. fee schedule committee, to succeed Doctor Harold P. Totten, resigned.

Adjournment.

SIDNEY J. SHIPMAN, M.D., *Chairman.*
L. HENRY GARLAND, M.D., *Secretary.*

212th Meeting

The meeting was called to order by Chairman Shipman at the Family Club, San Francisco, at 5:30 p.m., Wednesday, September 29, 1948.

1. *Roll Call:*

Present were President Askey, President-Elect Kneeshaw, Speaker Alesen, Council Chairman Bruck and Auditing Committee Chairman Shipman, chairman of the committee.

Present, ex-officio, were Secretary-Treasurer Garland and Editor Wilbur.

Present by invitation were Executive Secretary John Hunton; Legal Counsel Howard Hassard; Field Secretary Ed Clancy; executive secretary of the Public Health League of California, Ben H. Read.

Present by invitation during a portion of the meeting were Col. Alvin Gorby, M.C., U.S.A.; Lt. Col. Stuart I. Draper, M.C., U.S.A.; Maj. Donald L. Brubaker, M.C., U.S.A. (U.S.A.F.), and Capt. E. J. Best, M.C., U.S.N.

A quorum present and acting.

2. *Physicians for Military Service:*

Doctor Bruck outlined conferences he had held with Col. Gorby and other officers of the Sixth Army relative to the need of the Army and other forces for medical officers, both present need and anticipated demand under the enlarged forces under the new Selective Service Act. Col. Gorby stated that the present needs of the Sixth Army are for 31 additional medical officers by December 1, 1948, and an additional 60 by January 1, 1949. He stated that the Army tables of organization call for 4.7 physicians per 1,000 active personnel. Capt. Best stated that the Navy now needs 40 additional medical officers in the Twelfth District and 39 in the Eleventh District. Maj. Brubaker stated the Air Force relies on the Army Surgeon General for medical officers but pointed to a need of an unspecified number of medical officers in the near future.

Doctor Bruck reported that the suggestion had been made that the Association work with the armed forces in a campaign to cover the medical schools and teaching hospitals of the state in an effort to recruit young physicians for the military forces. There are now about 4,000 physicians or medical students in the U.S. who have received all or a part of their medical education at federal expense; of this number, only 216 are within the age limits of the Selective Service Act. After discussion, it was regularly moved, seconded and voted that the Association cooperate with all branches of the armed forces in a recruiting program for medical officers throughout the state, the Chairman of the Council to be authorized to activate this program.

3. *Memorial for Philip K. Gilman, M.D.:*

Discussion was held on the establishment of a memorial fund in the Stanford University Medical School in honor of the late Philip K. Gilman, M.D. It was regularly moved, seconded and voted that Doctor Wilbur ascertain from the school the manner in which such a fund might be established and report to the next Council meeting.

4. *State Department of Public Health:*

Doctor Shipman reported on a request received from the State Department of Public Health for assistance in a study to be conducted on methods of control for tuberculosis. Doctor Shipman suggested to the department that a representative of the Association be named on the study committee and the department has requested that such a representative be named. It was regularly moved, seconded and voted that Doctor H. Gordon MacLean be named as the Council representative on this committee.

5. *Public Policy and Legislation:*

An appeal for Association support of Proposition No. 5 on the November ballot was presented. This proposition would increase the salaries of members of the State Legislature from $100 to $250 per month. As an aid in attracting qualified men to serve as members of the Legislature, it was regularly moved, seconded and unanimously voted that the Executive Committee go on record as approving this ballot proposition and that the appropriate members of the Legislature be so notified.

6. *Santa Fe Hospital Association:*

In response to questions, Mr. Hassard reported on the present status of the controversy between members of the staff of Santa Fe Hospital Association, Los Angeles, and the trustees of the hospital. No further action has taken place since the Railway Mediation Board in Chicago declined to intervene in behalf of some physicians who had been dismissed or whose activities had been curtailed by the hospital trustees. It was pointed out that the Board of Medical Examiners, acting under a recent ruling of the State Attorney General relative to corporate practice of medicine, might take steps which could clarify this situation.

7. *Chronic Disease Study—Cancer Commission:*

Doctor Bruck reported that the chronic disease studies of the State Department of Public Health

have progressed to the point where proposed reports on the various sections of the study are under preparation. Members of the C.M.A. Cancer Commission are cooperating in the preparation of the cancer section of the report and Doctor Bruck has been named a member of a committee to edit all proposed sections of the entire report prior to presentation of the report to the entire committee for approval for presentation to the Legislature. If advisable, minority reports may be prepared.

8. *California Physicians' Service:*

Mr. Hassard and Doctor Cooley discussed the proposed plan of the Blue Cross and Blue Shield plans to cooperate in formation of a national organization to underwrite, through local plans, a nationwide coverage of prepayment medical care and hospitalization service. Physicians in some states are opposing this proposal and Mr. Hassard was authorized to meet with these physicians in Chicago on September 30, 1948, in order to advise them that the Executive Committee of the Association has reviewed the proposals and believes them to be sound and workable in principle.

9. *American Medical Association—General Practitioner Award:*

A communication from the A.M.A. outlining the methods to be used in selecting the physician to be honored by award of a token as the outstanding general practitioner of the year, was read and it was agreed that the county medical societies be notified of the eligibility of nominations and specifically notified that, because of the fact that all nominations must be in the hands of the A.M.A. prior to the November 30, 1948, interim session of the A.M.A. House of Delegates, the selection of a possible nominee from California must be made by the Council and not by the House of Delegates.

Adjournment.

SIDNEY J. SHIPMAN, M.D., *Chairman.*
L. HENRY GARLAND, M.D., *Secretary.*

Marysville Postgraduate Seminar

The first autumn postgraduate seminar of the series being conducted by the Committee on Postgraduate Activities of the California Medical Association was held at Marysville, October 1. The program consisted of a morning clinical conference on nephritis conducted by Dr. Marcus A. Krupp of the Veterans Administration, San Francisco, with presentations of types of acute and chronic stages of the disease.

At the afternoon session, formal papers were read. Dr. Krupp presented the latest concepts of diagnosis and treatment of nephritis.

Dr. Rene Bine, Jr., of Mt. Zion Hospital, discussed the results of research investigations carried on in the University of California Hospital and Mt. Zion Hospital on the use of anticoagulants in the management of acute coronary disease. He stated that judicious use of Dicumarol and Heparin resulted in notable reduction in the complications of thromboembolic phenomena.

The management of allergic diseases was reviewed by Dr. Albert H. Rowe, University of California Medical School. Dr. Rowe's discussion and illustrative slides presented an excellent coverage of this very troublesome and confusing field of medicine. Hypersensitization and its varied manifestations were reviewed, and general and specific treatments outlined.

The evening session was a symposium on the management of common serious highway accidents, with three papers—"Internal Injuries to the Chest," by Dr. Paul Samson, assistant clinical professor of surgery, Stanford University School of Medicine; "Internal Injuries to the Abdomen," by Dr. Leon Goldman, associate professor of surgery, University of California Medical School; "Orthopedic Surgery: The Extremities," by Dr. Frederic Bost, associate clinical professor of orthopedic surgery, University of California Medical School.

Dr. Samson emphasized the importance of early, correct diagnosis and advocated conservative treatment pointed toward as rapid reestablishment of physiological relations as possible by early and repeated aspiration of hemothorax or hemopneumothorax; relief of severe intercostal nerve pain from severe fractures by judicious local blocking of the intercostal nerves rather than by unphysiological morphine sedation; restoration of lost blood; and, finally, decortication of organized clot and fibrin under proper conditions, four to six weeks after trauma, to favor reexpansion.

Dr. Goldman emphasized the importance of proper and adequate facilities for diagnosis and institution of early supportive therapy in injuries involving the abdomen. He listed as essential the Wangensteen suction apparatus, oxygen equipment, plasma and catheterization set-up, together with clinical and x-ray equipment and personnel to assist the emergency surgeon. Shock stages, important symptoms and the various organ systems were succinctly re-

viewed. Dr. Goldman said that radical surgical procedures are much more often requisite to proper handling of serious trauma to the abdomen than in thoracic injuries.

Dr. Bost reviewed the important orthopedic problems commonly encountered. His emphasis was upon proper early management of the complications of serious fractures. He warned against early introduction of foreign bodies in compound fracture reduction; and stressed debridement, immobilization, chemotherapy and antibiotic therapy together with proper physiological supportive and restorative management.

After these papers were presented two motion pictures were shown, "Compound Depressed Fracture of the Skull" and "Cholelithiasis with Common Duct Stone."

Attendance was 24 at the morning session, 50 at the afternoon meeting, and 31 in the evening.

Additional seminars are scheduled as follows:

Sunday, Nov. 7	Redding	Gastric Surgery, Obstetrical Difficulties, Myocardial Infarction and Psychosomatic Medicine
Tuesday, Nov. 9	El Centro	Gastro-intestinal Symposium including Biliary and Liver Diseases
Saturday, Dec. 4	Santa Barbara	To be announced
Tuesday, Dec. 7	Riverside	To be announced
Friday, Dec. 10	Monterey	Anemias — Maxwell M. Wintrobe, M.D., University of Utah.

In Memoriam

HANSEN, PAUL SCOTT. Died in Santa Barbara, September 26, 1948, aged 38, of poliomyelitis. Graduate of Northwestern University Medical School, Chicago, Illinois, 1938. Licensed in California in 1946. Doctor Hansen was a member of the Santa Barbara County Medical Society, the California Medical Association, and the American Medical Association.

✤

MELLINGER, WILLIAM J. Died in Santa Barbara, August 28, 1948, aged 61, of coronary thrombosis. Graduate of the Chicago College of Medicine and Surgery, Illinois, 1913. Licensed in California in 1919. Doctor Mellinger was a member of the Santa Barbara County Medical Society, the California Medical Association, and a Fellow of the American Medical Association.

✤

REICH, WILLIAM WALTER. Died in Berkeley, September 19, 1948, aged 48, after a heart attack. Graduate of Stanford University School of Medicine, Stanford University-San Francisco, 1929. Licensed in California in 1929. Doctor Reich was a member of the Alameda County Medical Association, the California Medical Association, and a Fellow of the American Medical Association.

✤

TILLMANNS, CARL SAMUEL JONATHAN. Died in Los Angeles, September 14, 1948, aged 65. Graduate of the Washington University School of Medicine, St. Louis, Missouri, 1907. Licensed in California in 1919. Doctor Tillmanns was a retired member of the Los Angeles County Medical Association, and the California Medical Association.

NEWS and NOTES

NATIONAL • STATE • COUNTY

CONTRA COSTA

Dr. George Degnan, member of the staff of the Contra Costa County Hospital, has been appointed acting medical director. Dr. Degnan is serving in the post vacated by the resignation of Dr. E. A. Merrithew who had been director for 35 years.

LOS ANGELES

Dr. C. Leonard Huddlestone, director of the department of physical medicine at the University of Southern California, was installed as president of the American Congress of Physical Medicine at a recent meeting of that organization in Washington, D. C.

* * *

Postgraduate medical courses in the control of infectious diseases will be held during the fall and winter months under the auspices of the Los Angeles City Health Department. The meetings, which are to be held in the State Building at 217 West First Street from 8 to 10 p.m., Thursday evenings through March 31, 1949, are being administered by the Department of Infectious Diseases, School of Medicine, University of California at Los Angeles, and University Extension of the University of California. There is no enrollment fee.

The program of meetings already scheduled follows:

October 21: The Public Health Service in the Control of Communicable Disease. Leonard A. Scheele, M.D., Surgeon General, U. S. Public Health Service, Washington, D. C.

October 28: Diagnosis of Fevers of Unknown Origin. Albert G. Bower, M.D., clinical professor of public health and preventive medicine, College of Medical Evangelists.

November 4: Streptococcal Infections. James N. DeLamater, M.D., assistant dean, University of Southern California School of Medicine.

November 18: (a) Meningogoccal Meningitis. (b) Meningitis as a Complication of Communicable Disease. Albert G. Bower, M.D.

December 2: The Pneumonias—Diagnosis, Management, Complications. Roger O. Egeberg, M.D., clinical professor of medicine, School of Medicine, U.C.L.A.

December 9: (a) Diphtheria. (b) The Differential Diagnosis of Infectious Mononucleosis, Septic Sore Throat and Vincent's Angina. Albert G. Bower, M.D., and Louis J. Fisher, M.D., assistant clinical professor of medicine, College of Medical Evangelists.

December 16: (a) Enteric Infections. (b) Typhoid Fever and Bacillary Dysentery. Evelynne G. Knouf, M.D., associate clinical professor of medicine, College of Medical Evangelists, and assistant clinical professor of medicine, U.S.C. School of Medicine.

January 6: Brucellosis. Charles M. Carpenter, M.D., professor of infectious disease, School of Medicine, U.C.L.A., and Leon Rosove, M.D., assistant professor of medicine, U.S.C. School of Medicine.

January 13: (a) Pertussis. (b) Influenzal Meningitis. William P. Frank, M.D., instructor in medicine, U.S.C. School of Medicine, and Charles M. Carpenter, M.D.

January 20: Influenza. Thomas Francis, Jr., M.D., professor of epidemiology, School of Public Health, University of Michigan.

January 27: Measles, Mumps, and Chickenpox—Diagnosis, Treatment and Complications. William J. Mitchell, M.D., assistant clinical professor, U.S.C. School of Medicine.

February 3: Poliomyelitis. Albert G. Bower, M.D., Norman B. Nelson, M.D., assistant dean and associate professor of preventive medicine, School of Medicine, U.C.L.A.

PLACER

Dr. Saul Ruby, formerly of San Diego, has been appointed health officer of Placer County. Appointment of Dr. Ruby was advocated by Dr. N. A. Dubin, president of a recently created health board which serves in an advisory capacity to the county board of supervisors.

SAN FRANCISCO

The University of California Medical Center received a total of $49,426 in research grants from the National Foundation of Infantile Paralysis for the seven-month period ending December 21, 1947, according to a report by the Foundation.

Two grants were received. One, a grant of $43,090, went to support work under the direction of Dr. Karl F. Meyer, director of the Hooper Foundation for Medical Research, to determine how polio virus and similar disease infections spread. Development of dependable and rapid tests for identification of the virus and diagnosis of the infection is another aim. The second grant, of $6,336, was made to the Medical School for the continuation of instruction in physical therapy.

* * *

As part of a drive to interest girls in a career of nursing, the Woman's Auxiliary to the San Francisco County Medical Society has awarded its first nursing scholarship to Lily Chin, an American girl of Chinese descent. She was chosen from among a large group of candidates because of an excellent scholastic record and an earnest ambition to become a nurse. She chose to take her training at the University of California School of Nursing. The scholarship pays her tuition for a three-year course.

* * *

Three new appointments to the faculty have been announced by Dr. Loren R, Chandler, dean of the Stanford School of Medicine. Dr. Henry S. Kaplan has been appointed professor of radiology, Dr. Alfred E. Maumenee chief of the division of ophthalmology, and Dr. John A. Luetscher, Jr., associate professor of medicine.

Dr. Kaplan, formerly a radiologist with the National Cancer Institute, succeeds Dr. Robert R. Newell who is setting up a teaching and research program in biophysics. Dr. Maumenee, formerly a member of the faculty of Johns Hopkins Medical School, was appointed to take the place of Dr. Hans Barkan who retired from the Stanford faculty last year. Dr. Luetscher also is a former member of the faculty at Johns Hopkins.

SAN JOAQUIN

Dr. H. S. Chapman, city physician for Stockton, last month resigned that post after 28 years' tenure. The resignation was accepted "with regret" by the city manager, who said that it would become effective when a replacement for Dr. Chapman could be found.

At the first two of eight scheduled meetings in the tenth annual fall series of the **Stockton Postgraduate Study Club,** Dr. R. Wartenberg, associate clinical professor of neurology at the University of California, spoke on Neurological Examinations in the Office, and Dr. Salvatore P. Lucia, professor of medicine at the University of California, discussed Common Blood Disorders—Indications and Contra-indications for Splenectomy. Dr. Henry Risford was chairman of the first meeting, Dr. Neill P. Johnson of the second.

Program for the remainder of the series as announced by Dr. C. A. Broaddus, chairman of the program committee, follows:

October 16: Dr. Frederick L. Reichert, professor of surgery at Stanford School of Medicine, "Treatment of Conditions Involving the Sympathetic Nervous System." Dr. Emil J. Gough, chairman.

October 21: Dr. Charles E. McLennon, professor of obstetrics and gynecology at Stanford School of Medicine, "Clinical and Roentgen Pelvimetry." Dr. Lauren L. Heston, chairman.

October 23: Dr. Carleton Mathewson, Jr., professor of surgery at Stanford, "Present Status of Vagotomy." Dr. W. T. Auld, chairman.

November 18: Dr. J. K. Lewis, "The Heart Clinic." This, the only clinical meeting of the series, will be held at the San Joaquin General Hospital. Dr. Louis Armanino, chairman.

December 9: Dr. Daniel G. Morton, "The Use of Endocrine Products in Obstetrics and Gynecology." Dr. E. P. Halley, chairman.

December 16: Dr. Claude S. Beck, professor of neurosurgery at Western Reserve University School of Medicine, "Surgery of the Heart with Special Reference to Revascularization." Dr. Broaddus will be chairman of this meeting which is also the annual meeting of the Study Club.

SAN LUIS OBISPO

Bubonic plague in pools of fleas taken from squirrels in the areas of San Luis Obispo County has been demonstrated in tests at the state laboratory, according to a report by the California Department of Public Health.

SONOMA

With public contributions lagging, members of the Sonoma County Medical Society plan to provide about $8,000 to underwrite the proposed **Sonoma County Community Blood Bank.** It was announced by the Society that members would contribute $100 each to help in setting up a locally controlled blood bank. This decision was reached at a meeting of the Society at which **Dr. John Upton,** chairman of the Blood Bank Commission of the California Medical Association, outlined the problems of establishing a community bank. Dr. Upton said that San Francisco, San Mateo and Sacramento had been successful in setting up locally controlled blood banks.

Agreement of the members of the Society to subscribe $100 per member followed revelation that only about $3000 of $25,000 sought for the project had been raised by public contributions. The Society said that although members' contributions would be made with the understanding that refunds might be expected if public subscription ultimately provided sufficient funds, the members are prepared to leave their money in the fund if necessary.

TULARE

Dr. Adolph Wallner of Van Nuys has been named director of the Tulare County Hospital to take the place of Dr. Austin Miller.

YUBA-SUTTER-COLUSA

A seminar held October 1 in Marysville under the direction of the **Committee on Postgraduate Activities** of the C.M.A. was "highly praised" by those who attended, according to a report received from Dr. Leon M. Swift, secretary of the Yuba-Sutter-Colusa County Medical Society. Several physicians from surrounding communities as well as members of the local society attended, it was reported.

GENERAL

A new booklet stating the new and revised **morbidity reporting requirements** of the U. S. Public Health Service, with instructions and samples of report forms, has been issued by the Federal Security Agency. The new reporting requirements, the FSA said, were set up in an effort to bring about uniformity and simplification in morbidity reporting. Copies of the booklet may be had from Federal Security Agency, Public Health Service, Division of Public Methods, Washington 25, D. C.

* * *

Physicians treating beneficiary members of **California Physicians' Service** have been given an extension of the time limit within which they may submit bills for payment. Formerly 90 days after the end of the month in which services were rendered, the time for submission of bills now has been increased to six months. **The improving financial position of C.P.S.** warrants the time extension, according to Dr. Chester L. Cooley, secretary of the C.P.S. board of trustees, who explained that the 90-day rule was put into effect at a time when it was necessary to keep closer abreast of the liabilities represented by bills for services rendered.

Bills submitted to C.P.S. more than six months after the end of the month in which the service was rendered cannot be paid, the announcement said. Physicians were urged not to wait until the end of a course of treatment to submit a bill to C.P.S., but to send a bill at the end of each month for the treatment given within that month.

The time extension applies only to medical care rendered after October 1, 1948. Bills for services that were performed before that time must be sent to C.P.S. within 90 days of the end of the month within which the service was rendered.

* * *

"Gastric Cancer" is to be the subject for discussion at a special dinner meeting to be held on December 13, at the Fairmont Hotel, at 6:30 p.m. The meeting is sponsored by some of the county medical societies in the San Francisco Bay Area in conjunction with the Gastric Cancer Committee of the National Advisory Cancer Council. The speakers and their subjects are:

Dr. John A. Morton, professor of surgery, University of Rochester, Rochester, New York, "New Horizons in Gastric Cancer."

Dr. George N. Papanicolaou, professor of clinical anatomy, Cornell University, New York City, "Exfoliative Cytology as Applied to Gastric Cancer."

Dr. Leo Rigler, professor of radiology, University of Minnesota, Minneapolis, "Radiology in the Gastric Cancer Problem."

Reservations can be made by sending a check for the cost of the dinner ($5.50) to Dr. Ralph T. Behling, Cancer Control Officer, District No. 5, U. S. Public Health Service, 237 Federal Office Building, San Francisco 2, California.

* * *

The seventh annual meeting of the **American Academy of Dermatology and Syphilology** will be held in Chicago from Saturday, December 4 through Thursday, December 9, it is announced by Dr. Earl D. Osborne, secretary-treasurer of the Academy. The principal session will be held at the Palmer House, with special courses in histopathology and mycology scheduled for Saturday and Sunday, December 4 and 5, at

the Medical Schools of the University of Illinois and Northwestern University. As in the past two years, teaching clinics will be held on the afternoons of Monday, Tuesday, and Wednesday, December 6, 7, and 8. A new feature is being added to the program this year consisting of informal discussion groups which meet at noon and 5:00 p.m. sessions. Special courses in histopathology, mycology, x-ray and radium therapy, mucous membrane lesions, bacteriology of the skin, industrial dermatoses, specific granulomata, and dermatoscleroses will be held under leaders in these various fields.

* * *

From a recent analysis of 100,000 surgical benefit claims of all ages made by a committee of the Actuarial Society of America, the *Connecticut State Medical Journal* has excerpted "a number of interesting statistics," which it reports as follows:

"Not all surgery is performed in hospitals: 2 per cent of operations on men were performed out of the hospital; 16 per cent for children; and 11 per cent for women.

"The average amount paid for out-of-hospital claims was less than one-third that for hospital surgery.

"It was found that for an appendectomy 30 per cent of the doctors charged less than $100; 50 per cent, less than $125; 80 per cent, less than $150; and 90 per cent, less than $165. Charges were generally higher for men employees than for women, thus reflecting the general practice of suiting fees to the ability to pay.

"Surgical fees were highest on the West Coast, with California leading. They were next highest in the Middle Atlantic states and lowest in the South Atlantic states. Eight operations accounted for most of the surgical claims. These were: tonsillectomy, appendectomy, benign tumor or cyst, hemorrhoidectomy, fracture, hysterectomy, herniotomy, and dilation of curettage." * * *

Eighteen outstanding medical teachers have been selected for the first Annual Scientific Assembly of the American Academy of General Practice to be held in Cincinnati, March 7, 8, and 9, according to announcement by the program committee. The names of the essayists and their subjects will be announced later.

Arrangements have been made to accommodate more than 2,000 members and their wives. Non-members of the Academy may attend the Assembly as guests on payment of a registration fee of $5. Only doctors of medicine may register. There will be no registration fee for members. A printed form for requesting hotel accommodations will be sent to all members later, the announcement said.

* * *

A meeting of the American Goiter Association will be held May 26-28 at Madison, Wisconsin, according to a recent announcement by the association.

* * *

Construction of a new 1,000-bed psychiatric hospital at Fort Funston, San Francisco, to serve veterans in Northern California is expected to get under way next year, the Veterans Administration reports. Acquisition of 200 acres of the military post for the hospital has been approved by the Administrator of Veterans' affairs.

* * *

Approximately 400 U. S. cancer control leaders are expected to attend the first annual National Cancer Conference, February 25-27, 1949, to be held in Mephis. The conference will be sponsored jointly by the American Cancer Society and the National Cancer Institute of the Public Health Service. Various phases of the cancer problem will be discussed at round-table forums. Participants will include outstanding doctors and scientists from all parts of the country in the fields of medicine, nursing, statistics, research and public health.

The Medical Faculty of the University of California will offer the following program of postgraduate courses for qualified physicians in 1949:

January 31 through February 4, all day

PSYCHIATRY FOR GENERAL PRACTITIONERS. A course intended to give the general practitioner some knowledge of the major psychoses, with discussions of what he should do when he sees such cases. The general concept and treatment of psychoneuroses will be discussed. The integration of psychiatry with other fields of medicine will be considered, and some of the material commonly known as psychosomatic medicine will be offered.

January 31 through February 4, all day

CARDIOLOGY. This course will cover some recent advances in the knowledge of diseases of the cardiovascular system, with clinical demonstrations and discussions.

In addition there will be evening sessions during the same week, on INTERPRETATION OF ELECTROCARDIOGRAMS. These evening sessions will constitute a separate course and can be taken separately or as a supplement to the course in CARDIOLOGY.

June 20 through 24, all day

ENDOCRINOLOGY, INCLUDING DIABETES. In this course emphasis will be placed on the clinical aspects, with instruction regarding diagnosis and management of endocrine diseases.

July 5 through 8, all day

OBSTETRICS AND GYNECOLOGY. This course will be offered to all physicians interested in this branch of medicine. An attempt will be made to cover those things which are important from a practical point of view, as well as to include some of the newer points of interest.

September 5 through 9, all day

OTORHINOLARYNGOLOGY. This course is a continuation of the course offered in 1947, and is intended for specialists.

September 12 through 16, all day

OPHTHALMOLOGY. This is a continuation of the course offered in 1947 and 1948, and is intended for specialists.

September 19 through December 5, every Monday evening

CONTINUATION COURSE IN GENERAL MEDICINE. This is a series of evening lectures for general practitioners. There will be twelve meetings of two hours each.

December 5 through 9, all day

DISEASES OF THE CHEST. Offered by the American College of Chest Physicians.

* * *

A national medical public relations conference, first of its kind, which will consider six issues facing the medical profession will be held in St. Louis November 27, Dr. George F. Lull, secretary-manager of the American Medical Association, announced. Public relations directors, executive secretaries charged with public relations duties and public relations committee chairmen from each of the 48 state medical societies will be invited. Carefully-selected discussion leaders from the state societies will grapple with these six major social issues facing the medical profession: selling the need of public relations to state medical society members, encouraging wider use of medical pre-payment plans, setting up workable systems for handling night calls, the rebate problem, developing good-will with labor, farm, industrial and co-op groups, and cooperating with health agencies.

The conference will immediately precede the annual secretaries-editors meeting, which is being held in conjunction with the annual Interim Session of the American Medical Association, November 28 to December 3.

INFORMATION

Summary of Information Regarding Some of the Newer Insecticides

The past few years have witnessed intense research in the development of new insecticides with resulting products such as DDT, DDD, chlordane and others which have proven to be a boon to the agricultural industry. However, these new compounds, besides being effective insect killers, are also toxic to humans and can be dangerous if improperly handled. Most recently a new group of compounds, the organic phosphates, has come into use and represents a potential threat to human beings.

Hexaethyl tetraphosphate (HETP) was developed in Germany and in that country was known as "Bladan." Tetraethyl pyrophosphate (TEPP), which is the active toxic ingredient in HETP, was independently developed at the University of Chicago a short time ago. Both these compounds are heavy, syrupy liquids freely miscible with water. On contact with moisture they readily hydrolyze and lose their toxicity; hence there is little residual action as in the case of DDT.

They are both extremely toxic to insects and animals, and very minute amounts (2-10 mgm/kgm) are fatal to experimental animals. Several cases of poisoning in humans have occurred in California and because of the increasing use of the compounds others will doubtless be reported.

Absorption—These products are freely absorbed from the gastro-intestinal tract following ingestion. In addition, experimentally, they are rapidly absorbed through the intact skin, a property which makes them extremely hazardous. They are only slightly irritating when first applied to the skin so that there is no immediate warning sign as to the potential danger. Instillation in the eye produces immediate local reaction. It is probable that they are also absorbed through inhalation of their vapors.

Pharmacology—HETP and TEPP act pharmacologically by causing an irreversible destruction of the enzyme cholinesterase. As a result of this action there is an accumulation in the body of acetyl choline with consequent symptoms of excessive parasympathetic nervous stimulation, producing both muscarine and nicotinic effects.

Symptoms—Symptoms of acute poisoning with these compounds are primarily those due to parasympathetic stimulation. There is marked pupillary contraction and spasms of the eye muscles of accommodation which may persist for two or three days, resulting in blurred vision and inability to focus on distant objects. There is frequently a feeling of tightness of the chest and observers have noted dyspnea, bronchial spasm and pulmonary edema resulting from capillary dilatation and excessive glandular secretions in the bronchi and bronchioles. The smooth muscle of the gastro-intestinal tract becomes spastic, causing vomiting, constipation or diarrhea, and abdominal cramps. The central nervous system is affected, causing excitement and sometimes convulsions, frequently followed by central nervous system depression.

Death in acute poisoning may be due to any one of the following mechanisms:

1. Bronchial constriction and cardiovascular collapse.

2. Central nervous system stimulation and eventual depression.

3. Stimulation and eventual depression of neuromuscular junctions.

4. Accidents occurring as a result of the visual or mental impairment.

Information regarding chronic toxicity and cumulative action is both incomplete and inconsistent. Experimental animals receiving sub-lethal doses have survived with no residual damage, presumably because they were able to reproduce enough cholinesterase to replace the amount destroyed by the insecticide. However, further studies on this point are necessary.

Diagnosis—At the present time diagnosis of intoxication with one of these compounds depends mainly on an awareness of the syndrome and on a high index of suspicion in areas where these chemicals are being used. Any person who may possibly have come in contact with these insecticides, complaining of "blindness," blurred vision, tightness of the chest or any of the other symptoms mentioned should be suspected of suffering from acute intoxication with an organic phosphate. The laboratory finding of reduced cholinesterase in the plasma is confirmatory evidence.

Treatment—Atropine protects against, and counteracts, the central and autonomic nervous system disturbances caused by these phosphates. Therapeutic doses (0.1 - 0.5 mgm/kgm) protect experimental animals against 3 to 4 lethal doses. Curariform agents, especially the magnesium ion, protect the myoneural junction against the nicotinic effects. The most effective therapy is a combination of atropine and magnesium.

Prevention—Poisoning by these compounds can be prevented if proper attention is given to safe methods of handling them and if all persons concerned appreciate fully their extreme toxicity. All contact with the bare skin must be avoided and im-

From the California Department of Public Health.

pervious gloves must be worn when handling the compounds. If any of the material gets on the skin it should be thoroughly washed off with copious amounts of soap and water. Inhalation of TEPP and HETP dust, mists and aerosols should be avoided by use of a mask approved by the State Division of Industrial Safety. Workers should change clothes completely and bathe with soap and water after using the material. Contamination of food and tobacco of course should be avoided. Any exposed person developing symptoms should immediately be removed from the exposure and should be seen by a physician as soon as possible.

Bureau of Adult Health—Physicians are urged to report cases of poisoning from insecticides to the Bureau of Adult Health, 2002 Acton Street, Berkeley 2, California. The Bureau is compiling such reports to be used as a basis for study of the problem. The Bureau's personnel and facilities are available to physicians for assistance in the diagnoses of these cases.

Another organic phosphate which is coming into widespread use is Parathione. Since this compound differs somewhat chemically and pharmacologically from HETP and TEPP, it will be discussed in a future bulletin.

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3. Dayrit, C., Manry, C. and Seevers, M.: Pharmacology of hexaethyl tetraphosphate, Journal of Pharmacology and Experimental Therapeutics (Feb.), 1948.

Lion Roars Less Loudly

[*Reprinted from the New England Journal of Medicine.*]

The Comitia of the Royal College of Physicians, acting in a spirit of sweet reasonableness, has forwarded two resolutions to the minister of health, Aneurin Bevan, vociferous sponsor of the National Health Service Act of 1946. The first suggests that an act be brought in by the minister of health amending the National Health Service Act of 1946 by discarding full-time medical service by regulation. The second recommends a bill to make regulations affecting the National Health Service subject to special parliamentary procedure rather than to ministerial dictation alone.

Mr. Bevan, departing from his accustomed role, has apparently listened to the voice of the British Medical Association as expressed in its plebiscite of January 31, in which it overwhelmingly rejected the National Health Service Act as it was originally written.

He has now proposed his own modifications of the Act. In these he relinquishes a full-time service to be brought into effect by regulation and also modifies the proposal for a universal basic salary, limiting such salaries to three years, after which the practitioner may make his own decision whether to continue with salary and capitation fee, or to continue with a capitation fee as the sole source of income from practice. These new proposals represent a considerable willingness to compromise, since even his own party is not entirely in sympathy with them.

The Government, according to Mr. Bevan's parliamentary secretary, now recognizes that a full-time salaried service is incompatible with free choice of physician by the patient; more, it recognizes the importance of the principle of free choice of physician and therefore puts forward the compromise of payment partly by capitation fee and partly by salary. Further, although the buying and selling of public practices will still be forbidden, every doctor will be free to practice where he wishes, except in professionally overcrowded areas, and will have the right to choose his partner or assistant.

A few strands of democracy will remain in Britain's anchor line, although, as the *British Medical Journal** phrases it, "Mr. Bevan's machinery may provide that justice will be done, but we doubt whether it will make it possible that justice 'may manifestly be seen to be done.'"

A plebiscite on the amendments proposed by the Government indicates that approximately 64 per cent of the British Medical Association members still disapprove of the Act, with 36 per cent approving. Only 52 per cent, however, are against serving under the Act whether they like it or not, a majority so bare that further organized resistance seems impossible.

There is no question that, with Britain's peculiar genius for compromise, the doctors of England will now unite in an organized effort to make the new system effective.

*Editorial. Plebiscite, Brit. M. J., 1:791-793, 1948.

BOOK REVIEWS

CORRELATIVE NEUROANATOMY. By Joseph J. McDonald, M.S., M.D., Joseph G. Chusid, A.B., M.D., and Jack Lange, M.S., M.D., fourth edition, revised. 60 illustrations. University Medical Publishers, Palo Alto, 1948. $3.00.

This work, which is in outline form, comprises descriptions of the peripheral nerves and the automatic nervous system, the spinal cord and the brain. It attempts to establish correlations between the anatomy and physiology of these structures and the symptoms and signs encountered in many neurological syndromes. It also presents an outline for a neurological examination and a resume of data concerning electroencephalography.

This book is not a substitute for the standard textbooks on neurology. It should provide a means, however, of presenting to students certain bald facts around which can be built a substantial structure of useful knowledge. Its chief value will be to undergraduate students preparing for examinations and to candidates for state board examinations and American board examinations which demand a reasonable amount of neurological information.

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DIAGNOSTIC PROCEDURES FOR VIRUS AND RICKETTSIAL DISEASES. First edition. Publication Office American Public Health Association, 1790 Broadway, New York City, New York. 352 pp., 20 illustrations. $4.00.

This volume has been prepared by a group of outstanding authorities and is designed to present "a collection of laboratory methods at present applicable to the diagnosis of virus and rickettsial disease in man." This aim has been most satisfactorily attained, the many complicated procedures being intimately described. No experienced laboratory worker should have difficulty in the establishment of the various techniques by following the outlines presented in this book.

The material is presented in 16 sections, each of which is introduced by a brief description of an infectious agent and the human diseases caused by it. Isolation of the virus or rickettsia, and immunological methods useful in the study of infected human beings are then considered in great detail. The subjects covered are psittacosis, lymphogranuloma venereum, trachoma, inclusion blennorrhea, variola and vaccinia, influenza, primary atypical pneumonia, mumps, poliomyelitis, encephalitis, rabies, herpes simplex, yellow fever, dengue, phlebotomus fever, and the rickettsial diseases.

The technical material will not be of great value to clinicians but the book should be read in part by all physicians. The excellent brief descriptions of viruses and virus diseases will be of interest. In addition, the extreme complexity of virus isolation and immunological diagnostic techniques is emphasized. Too often a request for "virus studies" is made by the clinician who has insufficient understanding of the magnitude of the laboratory investigation which he has suggested.

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MODERN CLINICAL PSYCHIATRY. By Arthur P. Noyes, M.D., Superintendent, Norristown State Hospital, Norristown, Pennsylvania. Third Edition. W. B. Saunders Company, Philadelphia and London, 1948. $6.00.

This standard textbook of psychiatry has been brought up to date in a fairly satisfactory manner without changing its orientation or style of presentation in any significant degree. The author's approach is the eclectic one, which is admirable, but sometimes the reader is left without much direction regarding varying points of view. The recent advances in treatment have been adequately covered.

The method of presentation is formalized along traditional lines, and is particularly suited to the wants of the student who feels the necessity of strict classification of clinical syndromes. The amount of case material is adequate for illustrative purposes,

In all, the book is useful to the student or physician who desires a concise presentation of the psychiatric conditions to be seen in hospital practice, but relatively weak in its presentation of the minor reaction types which constitute the great share of psychiatric material seen by the internist and general practitioner.

* * *

THE TREATMENT OF MALIGNANT DISEASE BY RADIUM AND X-RAYS, BEING A PRACTICE OF RADIOTHERAPY. Ralston Paterson, M.C., M.D., F.R.C.S.E., D.M.R.E., F.F.R. Christie Hospital and Holt Radium Institute, Manchester. The Williams and Wilkins Company, Baltimore, 1948.

This is a practical and well written book on modern radiation therapy, compiled with the assistance of various authorities, including Margaret Tod, Meredith and others. It stresses the present method of treatment as used at the Radium Institute in Manchester, and is replete with data on the use of radium molds and needles, and radon implants. Diagrams of radium set-ups are shown, and radiographs of the actual placement of radium in different cases are reproduced.

The x-ray treatment of malignant lesions is also presented but not in as much detail as is accorded radium. Paterson apparently still prefers radium for many types of case which could now be treated with low voltage x-ray or contact x-ray in this country. Indeed, contact x-ray is but briefly considered. Radioactive isotopes are mentioned only in passing.

Unfortunately no statistics are given as to the results of treatment following his methods and the reader is referred for these to the reports of the Holt Radium Institute.

Paterson stresses careful positioning of the patient, and the importance of meticulous care in maintaining position for x-ray treatments. Casts of plaster or plastic are individually fitted. Markers are put in place and films taken to accurately center the lesion from various ports. The tumor may first be outlined with inactive radon seeds or by the introduction of barium! Back pointers and large protractors are used to direct the beams through the previously localized ports. Considerable detail is included in the chapter on field selection and volume dose.

Tables are included for radium dosage using various applicators, and practical rules for distribution and dosage are discussed. There is a chapter on making radium molds. All the detail, however, only emphasizes the need for first hand instruction and practice.

Paterson adds x-ray roentgen and gamma roentgens for total depth dose calculation, but notes that from a biological viewpoint they cannot be summated. He brings out the importance of the time interval in relation to the field size and dose. Many writers tend to mention this briefly, if at all, but it is extremely important for the end results. Paterson indicates that similar results may be obtained with many different techniques and that there are few hard and fast rules in roentgen therapy. However, he suggests certain general types of plan and tends to treat his cases according to one of these plans, for example: 1 day radical or palliative therapy, 4 day palliative, 8 day palliative, 8 day radical, 18 day, 32 day and indefinite period plans. In skin tumors, for instance, small lesions up to 3 cm. in size can be treated with 1750-2000 r in a single session, or by any one of the above

mentioned time intervals with appropriate change in total dosage. He does not stress the ultimate cosmetic benefit of protection in skin lesions.

He stresses the importance of the *tumor dose* instead of the total air r, or r on skin so often found in the radiological literature.

Although all of Paterson's methods are not universally accepted as ideal, he does present a thorough and clear summary of treatment as found to be most efficacious for his organization. The radium studies are particularly useful and seem better presented than the x-ray. The chapters on the uterus and breast seem less adequate than those on the skin and oral structures.

This book is well worth including in the library of every radiologist.

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DISEASES OF THE EAR, NOSE AND THROAT. By William Wallace Morrison, M.D., Professor of Otolaryngology and Attending Otolaryngologist, New York Polyclinic Medical School and Hospital. Appleton-Century-Crofts, Inc., New York, 1948. $8.50.

While this book is written largely for the use of the undergraduate student and the general practitioner, it is worth a place on the shelf of the otolaryngologist. The simplicity and clearness of the descriptions show the result of the author's long teaching experience. The absence of color plates would seem to detract from the value of the book but the author's drawings illustrate to an unusual degree the subject matter so that color plates seem unnecessary.

The short chapter on history-taking is of especial value to the student.

The descriptions of operative technique and bronchoscopy are not very complete, but are adequate for the purpose for which the book is intended.

Among the new features which are of considerable value are the chapters on local anesthesia, vasoconstrictor drugs, antibiotics, audiometry, aero-otitis, endaural surgery, the use of radium in the nasopharynx, Meniere's syndrome, allergy, headaches and laryngotracheobronchitis. Many more new features with a complete description of all recognized procedures in the practice of otolaryngology make the book very much worth while.

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VENOUS THROMBOSIS AND PULMONARY EMBOLISM. By Harold Neuhof, M.D., Clinical Professor of Surgery in Columbia University; Consulting Surgeon to Mount Sinai Hospital, Montefiore, Beth El, and Hackensack, N. J., Hospitals. Mt. Sinai Monograph No. 2. Grune and Stratton, New York, 1948. $4.50.

This monograph is based on the author's wide experience with venous thrombosis and pulmonary embolism at the Mount Sinai Hospital in New York City. It is divided into two parts. The first deals with various forms of venous thrombosis and pulmonary embolism, with illustrative case reports. Emphasis is placed on thrombectomy with vein ligation in the surgical treatment of this condition.

Although anticoagulant therapy is mentioned, it is not adequately described or discussed.

The second part of the book is devoted to an analysis of 88 proven cases of fatal pulmonary embolism which occurred in the period between January 1, 1928, and April 1, 1938. There are excellent clinical descriptions with a correlation of the postmortem findings. The author emphasizes the fact that "there is no constant relationship between the degree, location and extent of the pulmonary embolism and the clinical syndrome produced."

The chief value of this book lies in the clear description of the clinical cases of pulmonary embolism. It is recommended for those physicians who are particularly interested in the finer points in diagnosis and pathology of this condition.

HUMAN NUTRITION. By V. H. Mottram, M.A. (Cant.), formerly Professor of Physiology King's College of Household and Social Science, University of London. Williams and Wilkins Company, Baltimore, 1948.

Although Mottram's fascinating and interesting volume is small, it is one of the most important contributions on human nutrition available to English-speaking peoples. The book, a primer of nutrition, emphasizes the biochemical and metabolic values of food in maintaining the human economy in optimum condition. Man is what he eats, and Mottram indicates why.

There are interesting chapters on the fundamentals of dietetics where the functions of food are stressed and a plea made for a mixed diet—one which will ensure the necessary elements for growth, maintenance, and repair. The chapter on digestion and metabolism presents the physiology of these important processes with simplicity and clarity. There is an excellent discussion of the *biologic value* of proteins, and the part they play in nutrition. The chapter on the importance of mineral elements is extremely practical. In another chapter the *optimal diet* is discussed in great detail from both the experimental and theoretical viewpoints. There is an informative chapter on cooking and processing of foods and how these factors influence nutritive value. Another chapter devoted to an exploration of the lore of meal habits shows the relationship between the time of taking meals and maximum muscular efficiency.

The last chapter of the book, dealing with the nature of foods, is a classic and should be read by everyone. It is a valuable book for the physician, and it is delightful reading.

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PRINCIPLES GOVERNING EYE OPERATING ROOM PROCEDURES. By Emma I. Clevenger, R.N., Supervisor Eye Operating Room, New York Eye and Ear Infirmary, New York City. The C. V. Mosby Company, St. Louis, 1948. $5.50.

This book is well done and covers the field thoroughly. It follows the pattern of the methods used at the New York Eye and Ear Infirmary.

The book gives all procedures before, during and after operations on the eye. Part III, enumerating eye operations and the instruments used, is very instructive.

This book should be a must for any hospital having a department of ophthalmology. Both nurses and doctors can greatly benefit by reading it.

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TUBERCULOSIS, A Discussion of Phthisiogenesis, Immunology, Pathological Physiology, Diagnosis, and Treatment. By Francis Marion Pottenger, A.M., M.D., Emeritus Professor of Medicine, University of Southern California, The School of Medicine. Illustrated. The C. V. Mosby Company, 1948.

Dr. Pottenger, an elder statesman among chest physicians in California, presents in this book his views concerning many aspects of tuberculosis. Adequate references are made to the literature for general orientation, but the emphasis is on Dr. Pottenger's own views and contributions.

The chapters on pthisiogenesis are confusing, containing vague references to toxins, enzymes, cellular excitation, general body excitation, etc. The known facts concerning the immune response to tuberculosis are not clearly presented, and the important contributions of Rich, Raffel, and others are virtually ignored.

The most unusual feature of the book is its emphasis on visceral neurology in relation to tuberculosis. Dr. Pottenger has made important contributions to this subject, and his detailed presentation of signs and symptoms caused by involvement of the vegetative nervous system is worth reading. To most physicians, the interpretation placed upon minor alterations in palpation and percussion will seem

somewhat esoteric. To quote one example: "Palpation and percussion showed enlarged hilum structures on both sides, with slight infiltration in both apices, more marked on the right. The right side showed considerable lagging and the apical muscles on both sides were slightly degenerated, and also in spasm. The apical process, however, did not seem to be sufficiently active to account for the symptoms."

Treatment is dealt with in a conventional manner, although Dr. Pottenger's enthusiasm for tuberculin therapy will not be shared by all.

For the student interested in a clear, objective orientation in the field of tuberculosis, this book cannot be recommended; the recent works of Rich and of Pinner are much more suitable. However, for the specialist who is acquainted with the literature and able to form his own judgments, Dr. Pottenger's viewpoint will prove stimulating.

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HUTCHISON'S FOOD AND THE PRINCIPLES OF DIETETICS. Revised by V. H. Mottram, M.A. (Cant.). Sometime Fellow of Trinity College, Cambridge, and Late Professor of Physiology at King's College of Household and Social Science, University of London, and George Graham, M.D. (Cant.), consulting physician to St. Bartholomew's Hospital. Tenth edition. The Williams & Wilkins Company, Baltimore, 1948. $6.75.

This is an encyclopedic volume dealing with the biochemical and nutritive value of foods and the physiology of digestion and metabolism. The first five chapters of Section I deal with the subject of diet in normal life, and cover the fundamental divisions of the field of nutrition, namely those dealing with energy; body building materials; the minerals, with emphasis placed on the importance of the significant ones. There is an excellent chapter on the historical and evolutionary background of the vitamins.

The next four chapters are devoted to the practical aspects of nutrition, emphasizing the optimal diet and its availability and the processing, storage, cooking, and protection of foods. The section closes with two chapters devoted to the physiology of normal nutrition, where the topics of digestion, absorption, and metabolism in health are given in considerable detail. A short chapter on the subject of food habits closes the section.

Section II deals with the nature of foods. The chapter on foods used for energy is very good and contains an excellent discussion of the cereals and a detailed analysis of breads and the potato. Two chapters in this section are devoted to the proteins, which are presented from the point of view of their biologic value, eggs heading the list, followed by milk and milk products. Another chapter deals with the foods prominent because of their mineral and vitamin contents. A short chapter deals with the subject of flavors and condiments, and the last chapter with beverages—water, tea, coffee and alcohol. The latter is a dispassionate presentation of information on the subject which is aimed at dispelling the uncritical preconceptions of the clinician.

Section III is devoted to the clinical principles of feeding in infancy and childhood. The subjects of substitutions for human milk, and proprietary foods are covered in detail. Section IV deals exclusively with the clinical problems involved in the use of diet in disease. The discussions of diet in the treatment of fevers, obesity, and constipation are very good. The sections dealing with diabetes, arthritis, renal calculus and anemia could be improved. The topics of anorexia nervosa, gout, osteomalacia, peptic ulcer, gastrointestinal disturbances, sprue, cirrhosis, cardiac failure, epilepsy, and the nephritides are covered with reasonable adequacy. And the final chapter gives a critical analysis and evaluation of the problem of artificial feeding.

This book is highly informative and well written. The sections which deal with the fundamental subjects of chemistry, physiology and metabolism are among the best in the field, and they far overshadow the clinical sections. The bibliography is very well chosen, pertinent and good. The table of contents is unusually full and descriptive of the text and combined with the index makes the book extremely easy to use.

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WAR, POLITICS, AND INSANITY. By C. S. Bluemel, M.D., The World Press, Inc., Denver, Colorado, 1948. $2.00.

The first chapters of this small book deal with an explanation of some psychological terms applied to personality, and a consideration of these personality traits as they appear in great personages of history, in particular the conquerors and dictators. The author's thesis is that rather than our choosing our leaders for desirable characteristics, they force themselves on us because of their aggressive and compulsive natures. The last chapters deal with a possible solution to this problem in a democracy. The whole work seems quite superficial, and seems to bear out very well the statement of Dr. Walter Schaller, that psychiatrists are spreading themselves so thin that even their patients are beginning to see through them.

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ATLAS OF PLASTIC SURGERY. By Mortor I. Berson, M.D., formerly director of the Department of Plastic and Reconstructive Surgery, the Downtown Hospital and Pan-American Clinic, New York City. Grune and Stratton, 1948. $15.00.

This is a book of 304 pages including the index. It begins with a diagrammatic representation of some of the procedures of plastic surgery and continues with short explanations of these various procedures as applied to the different parts of the body.

The text is very limited, as might be expected in an atlas, and often omits important factors in operation. The book is not well balanced in its attempt to cover the field of plastic surgery. For instance, six pages are devoted to reconstruction surgery of the hand and only four cases are illustrated. One of these is at fault in that a diagram of an already placed abdominal flap on the dorsum of the hand is shown in a drawing as completely dissected from the hand except at the line of the scar at the wrist. Such dissection would result in complete loss of this flap because blood supply would not be possible. In addition, the photograph of the final result in this case is taken at an angle instead of a full anteroposterior view so that the true result is not shown in the region of the webs of the fingers which, of course, it is supposed to illustrate. There are no illustrations or discussions of tendon surgery or nerve surgery of the hand. In comparison, there are 66 pages devoted to reconstruction surgery of the nose, the great majority of which illustrate so-called cosmetic surgery.

In a few illustrations of actual cases by the author there is a lack of final pictures. In reconstruction of the ear by the reviewer's method, as so captioned in the book, the author has missed some of the important steps in the operation and the reviewer does not like to be held responsible for the final result as shown in the photograph.

Of the two photographs of finished reconstruction of harelips showing repair of the original deformity, that of the repair of the bilateral cleft lip is utterly worthless as a photograph because it is badly out of focus or something has happened to the film so that the result cannot be seen.

For the untrained in plastic surgery too much is omitted and the problems are made to appear so simple that one would think he need only follow the diagrams of the Atlas to obtain easy results. The book will add nothing to the armamentarium of the trained plastic surgeon.